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TESIS DOCTORAL

Aspectos relevantes en el seguimiento clínico y hemodinámico de pacientes con estenosis aórtica severa sintomática tratados mediante implante transcatéter de prótesis aórtica

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PRESENTADA POR

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Tesis Doctoral:

"Aspectos Relevantes en el Seguimiento Clínico y Hemodinámico de Pacientes con Estenosis Aórtica Severa Sintomática Tratados Mediante Implante Transcatéter de Prótesis Aórtica"

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INFORME DE LOS DIRECTORES DE LA TESIS

La presente tesis presentada según la normativa de compendio de publicaciones, recoge tres artículos originales y un artículo de revisión sistemática. Todos ellos han sido publicados en revistas indexadas en Pubmed y han sido sometidos a "revisión por pares". El trabajo de investigación se ha llevado a cabo mayoritariamente durante la estancia de dos años de la doctoranda en el prestigioso centro de Cardiología *Quebec Heart and Lung Institute* (Quebec, Canadá). En dicho centro, se desarrolla un programa ampliamente consolidado de implante transcatéter de válvula aórtica (TAVR, -del inglés *"Transcatheter Aortic Valve Replacement"*-) en el que la doctoranda se integró tanto en su vertiente de asistencia clínica como investigadora.

La trascendencia de la los trabajos de investigación incluidos en esta tesis viene determinada por el hecho de aportar información novedosa sobre cuestiones no resueltas del TAVR. Así, la valoración del rendimiento hemodinámico de las nuevas válvulas que acceden al mercado resulta esencial para determinar si los pacientes pueden ser tratados con estos nuevos dispositivos en condiciones de seguridad. De igual forma, si se pretende expandir esta técnica a pacientes más jóvenes, es de gran importancia esclarecer los factores asociados con un mayor deterioro de la hemodinámica valvular. Además, es preciso atender a las características y peculiaridades de los procedimientos de TAVR en la población, cada vez mayor, de pacientes con degeneración de una bioprótesis aórtica implantada de forma quirúrgica. Por último, es de gran trascendencia clínica dilucidar los factores asociados con una mayor tasa de rehospitalizaciones tras un procedimiento de TAVR, pues permitiría la realización de un seguimiento más estrecho de los pacientes en riesgo de presentar un peor pronóstico.

La relevancia, originalidad y rigurosidad metodológica de los trabajos de investigación aquí recogidos viene refrendada por el alto factor de impacto de las

revistas en las que han sido publicados. Es especialmente reseñable la publicación de dos de ellos en el *Journal of the American College of Cardiology*, revista de mayor factor de impacto entre todas las referentes a la Cardiología (IF:17,759).

Para concluir, es importante remarcar que varios de estos trabajos han sido posible gracias a la colaboración entre varios centros europeos y americanos. Como se ha hecho en este caso, consideramos esencial promover en los jóvenes investigadores la creación de estas redes colaborativas para un mayor y más eficaz avance en el conocimiento.

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ABREVIATURAS Y ACRÓNIMOS

ACV: Accidente Cerebrovascular

AIT: Accidente Isquémico Transitorio

DHV: Degeneración de la Hemodinámica Valvular

EA: Estenosis Aórtica

ETE: Ecocardiograma Transesofágico

ETT: Ecocardiograma Transtorácico

FEVI: Fracción de Eyección del Ventrículo Izquierdo

HTA: Hipertensión Arterial

IAo: Insuficiencia Aórtica

IRC: Insuficiencia Renal Crónica

PPM: Desajuste Paciente-Prótesis (del inglés "Prosthesis-Patient Mismatch")*

SAVR: Reemplazo Quirúrgico de Válvula Aortica (del inglés *"Surgical Aortic Valve Replacement"*)*

TAVR: Reemplazo Transcatéter de Válvula Aortica (del inglés *"Transcatheter Aortic Valve Replacement"*)*

TC: Tomografía Computerizada

TCMC: Tomografía Computerizada Multicorte

VI: Ventrículo Izquierdo

ViV: Válvula dentro de Válvula (del inglés *"Valve in Valve")**

*Debido a su uso ampliamente generalizado tanto en la literatura científica en castellano como en inglés, en la presente tesis se empleará el acrónimo en inglés.

ÍNDICE

RESUMEN

El reemplazo transcatéter de válvula aórtica (TAVR) es una técnica consolidada para el tratamiento de la estenosis aórtica severa en pacientes inoperables o de alto riesgo quirúrgico. Además, de acuerdo con los últimos estudios aleatorizados, también puede ser una alternativa en pacientes seleccionados de riesgo intermedio. Aunque el pronóstico tras TAVR sigue mejorando, continua habiendo aspectos sin resolver en relación a las nuevas válvulas para implante transcatéter, los procedimientos de TAVR en pacientes con implante previo de bioprótesis aórtica quirúrgica (procedimientos "Valve in Valve" –ViV-), los reingresos hospitalarios tras TAVR y la durabilidad de las bioprótesis transcatéter. El propósito de los cuatro artículos que componen esta tesis es aportar información a estas cuestiones aún sin resolver en el campo del TAVR.

Artículo 1: "Self-expanding Portico Valve Versus Balloon-expandable SAPIEN XT Valve in Patients With Small Aortic Annuli: Comparison of Hemodynamic Performance."

El objetivo de este estudio fue comparar los resultados hemodinámicos de la válvula autoexpandible Portico con los de la válvula balón-expandible Sapien XT en un estudio de casos apareados con análisis en un laboratorio central de ecocardiografía. Para ello, se emparejó a 22 pacientes tratados mediante implante transcatéter de la válvula Pórtico de 23 mm con 40 pacientes tratados con la válvula Sapien XT de 23 mm, según los siguientes parámetros: área y diámetro medio del anillo aórtico por tomografía Computerizada (TC), fracción de eyección del ventrículo izquierdo (FEVI), área de superficie corporal e índice de masa corporal.

No hubo diferencias estadísticamente significativas entre ambos grupos en el gradiente residual medio, ni en el área valvular efectiva ni en la incidencia de insuficiencia aórtica moderada o severa residual. Asi, concluimos que la válvula

autoexpandible Portico muestra resultados hemodinámicos a corto plazo similares a la válvula balón-expandible Sapien XT.

Artículo 2: "Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement: Multicenter Registry."

El propósito de este estudio fue determinar la incidencia, cronología y predictores de deterioro de la hemodinámica valvular en una amplia población de pacientes sometidos a TAVR.

Este estudio multicéntrico incluyó a 1521 pacientes tratados mediante TAVR. El seguimiento medio fue de 20 ± 13 meses (mínimo de 6 meses), se realizaron ecocardiografías al alta, de 6 a 12 meses y anualmente con posterioridad. El DHV se definió como un aumento ≥ 10 mm Hg en el gradiente transprotésico medio durante el seguimiento en comparación con el ecocardiograma al alta.

La tasa media anual de progresión del gradiente transprotésico durante el seguimiento fue de 0,30 ± 4,99 mmHg/año. La incidencia de DHV fue del 4,5% durante el período de seguimiento y 2,8% en el seguimiento de 6 a 12 meses. La ausencia de terapia anticoagulante al alta hospitalaria, los procedimientos ViV, el uso de una válvula de 23 mm y un mayor índice de masa corporal se identificaron como predictores independientes de DHV. En conclusión, se detectó un aumento pequeño pero significativo de los gradientes tras TAVR, siendo los factores predictores los anteriormente descritos Por ello, son necesarios estudios prospectivos y aleatorizados para determinar si una terapia antitrombótica específica post-TAVR puede reducir la incidencia de DHV.

Artículo 3: Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction

El uso de las bioprótesis ha aumentado significativamente en detrimento de las válvulas mecánicas quirúrgicas. Considerando que tienen una durabilidad limitada, existe también la necesidad creciente de reemplazar o reparar esas bioprótesis cuando éstas se deterioran. La rápida evolución de la terapia valvular transcatéter ha demostrado que el implante de válvulas transcatéter en bioprótesis quirúrgicas fallidas es seguro y factible.

Revisamos la perspectiva histórica de los procedimientos transcatéter ViV, así como las principales dificultades del procedimiento y el pronóstico clínico asociado a esta nueva forma de tratamiento menos invasivo.

Los procedimientos transcatéter ViV presentan todavía algunos interrogantes en términos de seguridad que incluyen: una mayor tasa de mal posicionamiento de la válvula (especialmente en los casos de válvulas "stentless", cuyo mecanismo degenerativo suele ser la insuficiencia aórtica), también se asocian a un incremento en la incidencia de obstrucción coronaria durante el procedimiento y a gradientes transprotésicos elevados en el seguimiento (especialmente en válvulas quirúrgicas pequeñas). Además, existen muy pocos datos sobre la durabilidad a largo plazo de las prótesis tras un procedimiento de estas características. Por otra parte, parece que los resultados hemodinámicos pueden estar influenciados por el tipo de prótesis, obteniéndose mejores resultados hemodinámicos con válvulas diseñadas para funcionar a nivel supraanular que con aquellas colocadas a nivel del anillo.

En conclusión, incluso si los datos apoyan el uso de procedimientos ViV en la mayoría de pacientes, es necesaria una cuidadosa evaluación del caso por un equipo multidisciplinar antes de abordar un procedimiento de estas características. El seguimiento a largo plazo de los pacientes ya tratados y el aumento de la experiencia con estos procedimientos determinarán el rol exacto de las terapias transcatéter en el

tratamiento de pacientes con fallo de bioprótesis quirúrgicas.

Artículo 4: Incidence, Causes, and Predictors of Early (≤30 Days) and Late Unplanned Hospital Readmissions After Transcatheter Aortic Valve Replacement

El propósito de este estudio fue determinar la incidencia, causas y predictores de hospitalizaciones no planificadas tras TAVR.

Se incluyeron 720 pacientes consecutivos que sobrevivieron al procedimiento de TAVR en dos centros. El seguimiento medio fue de 23 meses. Se obtuvo la ocurrencia, cronología y causas de las hospitalizaciones en todos los casos. Se consideró como reingresos tempranos a los que ocurrieron ≤30 días y tardíos a los que ocurrían entre 30 días y 1 año post-TAVR.

Se registraron 506 reingresos no programados en 316 pacientes (43,9%) en el primer año post-TAVR, 105 pacientes presentaron rehospitalizaciones tempranas (14,6%). Los motivos de reingreso se repartieron entre causas no cardiacas y cardiacas en el 51% y 49% de los casos, respectivamente. Las causas no cardiacas en orden decreciente fueron: patología respiratoria, infecciosa y hemorrágica, mientras que las rehospitalizaciones de causa cardiaca se debieron a insuficiencia cardiaca y arritmias, fundamentalmente. Los predictores de reingreso temprano fueron: complicaciones hemorrágicas periprocedimiento, anemia, baja FEVI, y la combinación de anticoagulación y antiagregación al alta. Los predictores de rehospitalización tardía fueron: enfermedad pulmonar obstructiva crónica, enfermedad vascular periférica, insuficiencia renal crónica y fibrilación auricular. Las rehospitalizaciones tempranas fueron un predictor independiente de mortalidad durante el periodo de seguimiento.

En conclusión, casi uno de cada cinco pacientes fue rehospitalizado en el mes posterior al procedimiento, hecho asociado con un aumento de la mortalidad. Las causas de reingreso se repartieron entre etiología cardiaca y no cardiaca con patología

respiratoria e insuficiencia cardiaca como las principales causas en cada grupo. Las rehospitalizaciones tempranas se asociaron a complicaciones hemorrágicas del procedimiento y las tardías estuvieron más relacionadas con la patología basal de los pacientes.

ABSTRACT

Transcatheter aortic valve replacement (TAVR) is well-established for treating patients with symptomatic severe aortic stenosis deemed at high or prohibitive risk for surgical aortic valve replacement (SAVR). Also, according to recent randomized clinical trials, TAVR may also be an alternative to SAVR in selected intermediate-risk patients. Although TAVR outcomes continue to improve, concerns remain with respect to new transcatheter valves, valve in valve (ViV) procedures, readmissions after TAVR and valve durability. The purpose of the four papers composing the present PhD Thesis is to provide new evidence on these current issues.

Paper 1: "Self-expanding Portico Valve Versus Balloon-expandable SAPIEN XT Valve in Patients With Small Aortic Annuli: Comparison of Hemodynamic Performance."

The aim of this paper was to compare the hemodynamic performance of the self-expanding Portico and balloon-expandable Sapien XT valves in a case-matched study with echocardiographic core laboratory analysis. Twenty-two patients underwent TAVR with the Portico 23 mm valve and were matched for aortic annulus area and mean diameter measured by computed tomography (CT), left ventricular ejection fraction, body surface area, and body mass index with 40 patients undergoing TAVR with the 23 mm Sapien XT. There were no significant between-group differences in residual mean transaortic gradients and effective orifice area. Rates of severe prosthesis-patient mismatch were low and similar between groups. Similarly, no differences were found in the occurrence and severity of moderate-severe paravalvular leaks. We conclude that TAVR with the self-expanding Portico system yielded similar short-term hemodynamic

performance compared with the contemporary balloon-expandable Sapien XT system for treating patients with severe aortic stenosis and small annuli.

Paper 2: "Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement: Multicenter Registry."

The purpose of this large-scale registry was to determine the incidence, timing and predictors of valve hemodynamic deterioration (VHD) in a cohort of patients undergoing TAVR.

This multicenter registry included 1521 patients who underwent TAVR. The mean follow-up was of 20±13 months (minimum of 6 months) and echocardiographic exams were performed at discharge, at 6 to 12 months, and yearly thereafter. VHD was defined as a ≥10 mm Hg increase in transprosthetic mean gradient during follow-up compared with discharge assessment.

The overall mean annualized rate of transprosthetic gradient progression during follow-up was 0,30 ± 4,99 mmHg/year. The incidence of VHD was 4,5% over the follow-up period and 2,8% at 6- to 12-month follow-up. The absence of anticoagulation therapy at hospital discharge, a valve-in-valve procedure, the use of a 23mm valve and a greater body-mass index were identified as independent predictors of VHD.

In conclusion, there was a mild but significant increase in transvalvular gradients over time following TAVR. The lack of anticoagulation therapy, a valve-in-valve procedure, a greater BMI, and the use of a 23mm transcatheter valve were the factors associated with higher rates of VHD post-TAVR. Further prospective studies are required to determine whether a specific antithrombotic therapy post-TAVR may reduce the risk of VHD.

Paper 3: Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction

The surgical use of Bioprosthetic valve has increased significantly. Considering their limited durability, there will remain an ongoing clinical need for repairing or replacing these prostheses in the future. With the rapid evolution of transcatheter heart valve therapies, the feasibility and safety of implanting a transcatheter heart valve within a failed tissue surgical valve has been established.

We review the historical perspective of transcatheter valve-in-valve (ViV) therapy, as well as the main procedural challenges and clinical outcomes associated with this new less invasive treatment option.

Transcatheter aortic ViV procedures still include several safety concerns, such as a higher rate of valve malpositioning (especially in cases of stentless valves, with aortic regurgitation as the main mechanism of failure), the appearance of coronary obstruction during the procedure, and elevated transvalvular gradients (particularly in smaller surgical valves). Moreover, there are scarce data on long-term durability of transcatheter valves following valve-in-valve procedure. In addition, a valve-type effect influencing the hemodynamic results of valve-in-valve procedures, with a supraannular valve leaflet position serving as an important factor determining improved hemodynamics.

Even if current data supports the use of valve-in valve procedures for most patients, a thorough multidisciplinary heart team approach is strongly recommended for every patient considered for this type of transcatheter therapy. Long-term follow-up and increasing the worldwide clinical experience will be fundamental for establishing the exact role of valve-in-valve implantation for treating degenerative bioprosthetic valves.

Paper 4: Incidence, Causes, and Predictors of Early (≤30 Days) and Late Unplanned Hospital Readmissions After Transcatheter Aortic Valve Replacement

The aim of this study was to determine the incidence, causes, and predictors of unplanned hospital readmissions after TAVR.

A total of 720 consecutive patients underwent TAVR at 2 centers who survived the procedure, were included. Median follow-up was 23 months. The occurrence, timing, and causes of hospital readmission within the first year post-TAVR were obtained in all cases. Early and late readmissions were defined as those occurring ≤30 days and >30 days to 1 year post-TAVR, respectively.

There were 506 unplanned readmissions in 316 patients (43,9%) within the first year post-TAVR. Early readmission occurred in 105 patients (14,6%). Readmissions were due to non-cardiac and cardiac causes in 59% and 41% of cases, respectively. Non-cardiac readmissions included, in order of decreasing frequency, respiratory, infection, and bleeding events as the main causes, whereas heart failure and arrhythmias accounted for most cardiac readmissions. The predictors of early readmission were periprocedural major bleeding complications, anemia, lower left ventricular ejection fraction, and the combined presence of antiplatelet and anticoagulation therapy at hospital discharge. The predictors of late readmission were chronic obstructive pulmonary disease, peripheral vascular disease, chronic renal failure, and atrial fibrillation. Early readmission was an independent predictor of mortality during the follow-up period.

In conclusion, nearly one-fifth of the patients were readmitted early after hospital discharge, increasing the risk of mortality at follow-up. Reasons for readmission were split between non-cardiac and cardiac causes, with respiratory causes and heart failure as the main diagnoses in each group, respectively. Whereas early

readmissions were mainly related to periprocedural bleeding events, most late readmissions were secondary to baseline patient comorbidities.

INTRODUCCIÓN

I. ESTENOSIS AÓRTICA

1. DEFINICIÓN

Definimos la estenosis aórtica (EA) como una obstrucción a la salida del flujo sanguíneo desde el ventrículo izquierdo (VI) a la arteria aorta (1). Dicha obstrucción puede localizarse a nivel supravalvular, subvalvular o valvular. La EA supravalvular es, en la práctica totalidad de los casos, una entidad congénita. La EA subvalvular puede deberse a una obstrucción fibromuscular congénita o a una obstrucción debida a la proliferación del miocardio ventricular (miocardiopatía hipertrófica). La EA valvular es la causa más frecuente de EA en adultos y es a la que haremos referencia en la presente tesis.

Las causas más frecuentes de EA son las siguientes: congénita, reumática y degenerativa (también llamada EA calcificada o senil) **(Figura 1)**. Otras causas menos frecuentes de EA incluirían entidades patológicas como: Enfermedad de Paget, obstrucción por vegetaciones en la endocarditis infecciosa, Lupus Eritematoso Sistémico, alcaptonuria o EA secundaria a radioterapia. La EA es la valvulopatía más frecuente en Europa y Norteamérica, estimándose que la EA degenerativa afecta a entre un 2% y un 7% de la población mayor de 65 años (2,3), con prevalencias de hasta el 9,8% en sujetos de entre 80 y 89 años (4). La segunda etiología más frecuente de EA es la congénita, la cual sería predominante en sujetos menores de 65 años. Por último, debido a las mejoras en el acceso sanitario, la EA reumática es hoy una entidad poco frecuente en los países desarrollados.

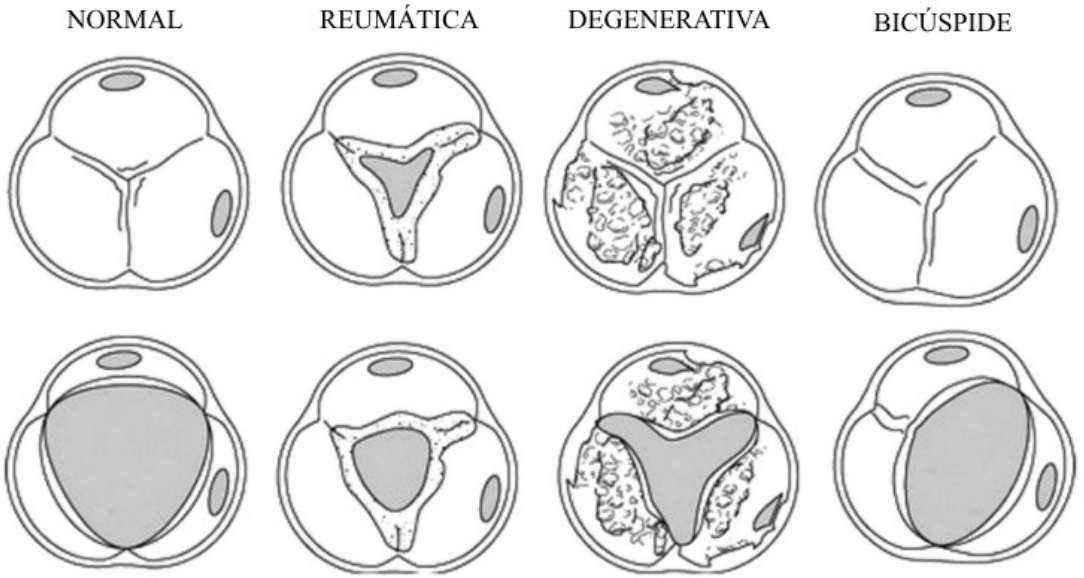

Figura 1: Diferentes Etiologías de EA (adaptado de Baumgartner et Al. (5)

2. EPIDEMIOLOGÍA

La calcificación de la válvula aórtica es un proceso frecuente, progresivo, y de gran relevancia clínica. En un estudio ecocardiográfico que englobó a 5621 sujetos mayores de 65 años, Otto y colaborares observaron una prevalencia del 29% de esclerosis aórtica definida como un engrosamiento irregular de los velos valvulares aórticos que no condicionaba obstrucción valvular. En este mismo estudio se evidenció que la esclerosis aórtica se asoció con un aumento significativo en la mortalidad cardiovascular y en la ocurrencia de infarto de miocardio (6). Numerosos estudios han demostrado que la incidencia y la prevalencia de EA aumenta con la edad (7). Así, según los datos ecocardiográficos obtenidos a partir de varios estudios poblacionales, la prevalencia de EA se estima en el 0,1% entre 45-54 años, 0,2% entre 55-64 años, 1,3% entre 56-74 años y 2,8% en los sujetos con ≥75 años (3).

Además, debido al aumento de la esperanza de vida y consecuentemente al envejecimiento poblacional, se ha demostrado que la prevalencia de EA se encuentra en aumento. Así, en un estudio que evaluó la prevalencia de enfermedad valvular en

Escocia, la incidencia de hospitalización con un primer diagnóstico de EA aumentó desde 246 casos por millón en 1997 hasta 365 casos por millón en 2005 (8).

3. FISIOPATOLOGÍA Y CLÍNICA

Aunque inicialmente se consideró un proceso degenerativo pasivo, actualmente se considera que la EA es un proceso activo que comparte mecanismos fisiopatológicos con la aterosclerosis vascular (9). Varios son los hechos que apuntan a esta vía etiopatogénica común:

- La lesión inicial en la EA comienza por una alteración endotelial debido al aumento de la tensión mecánica o disminución del "shear stress", de forma análoga a lo observado en lesiones ateroscleróticas coronarias tempranas (10). Así, los pacientes con válvula aórtica bicúspide, en los que se describe un mayor estrés mecánico a nivel valvular, tienden a presentar EA grave dos décadas antes que los pacientes con válvula aórtica tricúspide (11).
- Se demostró que animales alimentados con dietas ricas en colesterol desarrollan un proceso proliferativo similar a la aterosclerosis en la válvula aórtica que sería inhibido por la atorvastatina (12).
- Los factores de riesgo de la EA son similares a los que conducen a la aterosclerosis vascular (13).
- En la EA calcificada se encuentran marcadores de osteogénesis que se encuentran expresados en un nivel menor en las válvulas mitrales degenerativas (14,15).

La **Figura 2** (16) es una adaptación de la Figura 1 del artículo clásico de Ross y Braunwald en la que se muestra la reducción en la esperanza de vida en función de la aparición de los diferentes síntomas clásicos de EA. Hemos de reseñar que, aunque esta descripción de la historia natural de la enfermedad se ha considerado casi

paradigmática, la población de este artículo de 1968 dista mucho de la población actual con EA. En ella, las etiologías predominantes eran la reumática y la bicúspide, describiéndose una edad temprana de inicio de los síntomas (48 años) y altas tasas de mortalidad por endocarditis.

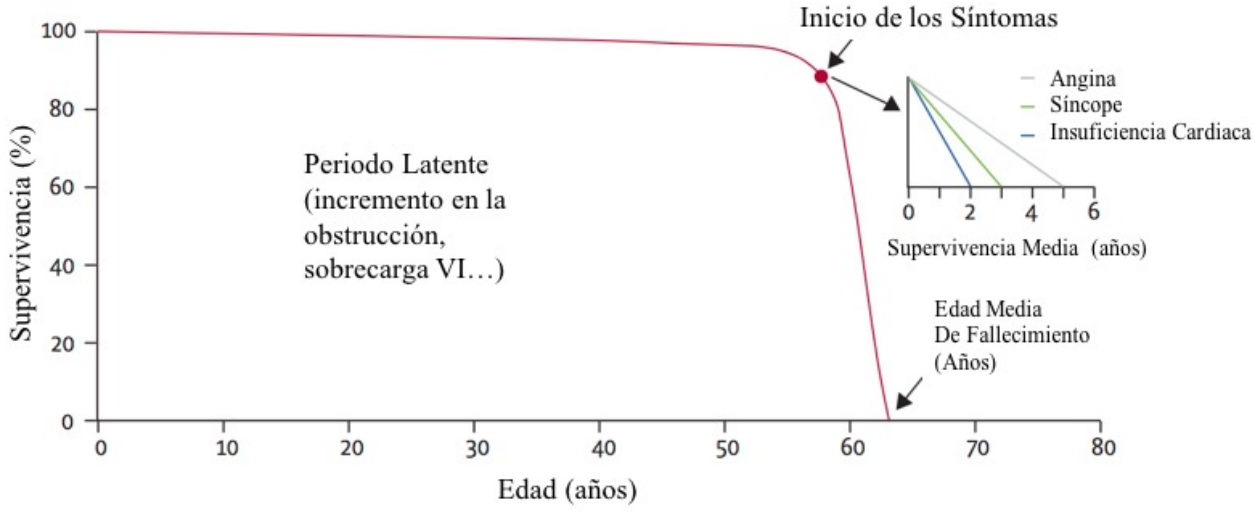

Figura 2: Supervivencia de los pacientes con EA en función de la aparición de síntomas.

Pese a que los tiempos de supervivencia clásicamente descritos puedan no ajustarse fielmente a la realidad actual, es un hecho generalmente aceptado que pacientes con EA asintomáticos tienen un buen pronóstico, aún en presencia de grados importantes de obstrucción. La aparición de síntomas, por el contrario, marca un punto de no retorno en el curso pronóstico de la enfermedad, estimándose una tasa de mortalidad del 25% por año en individuos sintomáticos (17). Es por tanto, de gran trascendencia clínica, comprender los mecanismos fisiopatológicos por los que se producen los considerados tres síntomas cardinales de la EA: angina, disnea y síncope.

El área valvular aórtica (AVA) puede reducirse hasta en un 50% de su superficie normal antes de que pueda objetivarse un gradiente transvalvular significativo (18). Posteriormente, una vez que puede medirse un gradiente de presión entre el VI y la aorta ascendente, se produce un aumento de presión en el VI. Este aumento de presión

progresivo provocará un aumento en el estrés de la pared del VI que llevará, en ausencia de corrección de la EA, a una disfunción ventricular izquierda. Sin embargo, antes de que se produzca un aumento en el estrés de la pared del VI, se ponen en marcha una serie de mecanismos compensadores, de los cuales el más importante es la hipertrofia ventricular (19). La hipertrofia del VI es proporcional al incremento de presiones ventriculares y hace que la masa ventricular izquierda alcance una media de 286 g/m^2 (20) en pacientes con EA (Vs 82 g/m^2 en la población control). La hipertrofia ventricular izquierda y la posterior tendencia a la taquicardia hace que las demandas miocárdicas de oxígeno estén aumentadas en la EA grave. En todos los demás lechos circulatorios, el suministro de oxígeno a los tejidos puede aumentarse tanto con un aumento del flujo sanguíneo como con un aumento en la extracción de oxígeno de la hemoglobina. El corazón es el único órgano que se irriga principalmente durante la diástole y en el que la extracción de oxígeno es siempre cercana al máximo. Por lo tanto, la única forma en la que el miocardio puede suplir el aumento en la demanda de de oxígeno es con un aumento del flujo sanguíneo coronario. En cualquier caso, pese a que el flujo coronario total está aumentado, debido a la hipertrofia, el flujo coronario indexado por cada 100 g de masa miocárdica está reducido (21). De esta forma, la perfusión subendocárdica está reducida en reposo (22), hecho que se acentúa aún más durante el ejercicio. En individuos sanos, la reserva de flujo sanguíneo en el ejercicio es del 500-800% respecto al flujo de reposo; sin embargo, en presencia de hipertrofia concéntrica, la reserva está disminuida, constituyendo únicamente del 200-300% del valor en reposo (21). Se cree que esta disminución podría ser secundaria a la disminución de los capilares en el miocardio hipertrofiado (23). Otros factores que contribuyen a la reducción en la perfusión coronaria en la EA serían la elevación en la presión telediastólica del VI y el efecto de “milking” acrecentado por la hipertrofia

ventricular. Como resultado de todo lo anterior, la angina de pecho es una de las manifestaciones cardinales de la EA severa, aún en ausencia de aterosclerosis coronaria significativa propiamente dicha.

El síncope es otro de los síntomas que ensombrecen el pronóstico en la EA. El mecanismo exacto por el que se produce aún no ha sido bien determinado, aunque parece ser independiente de la hipertrofia ventricular. Una de las posibles vías fisiopatológicas es que el aumento en el volumen de eyección que habitualmente acompaña al ejercicio está limitado en la EA debido a la obstrucción a la salida del ventrículo izquierdo. Por el contrario, la disminución en las resistencias periféricas se produciría de igual forma que en los individuos sanos, produciendo una caída en la presión sanguínea que llevaría al síncope en los pacientes con EA grave (24). También se ha propuesto que las elevadas presiones intraventriculares que se producen durante el ejercicio en la EA estimularían barorreceptores, causando un reflejo vasodepresor como respuesta (25). Por último, en algunos individuos, las arritmias ventriculares se verían favorecidas por la isquemia inducida en el ejercicio y podrían ser la causa del síncope (26).

Dado que los volúmenes ventriculares permanecen, inicialmente, estables, la hipertrofia ventricular se traduce en un engrosamiento significativo de la pared ventricular. Así pues, los pacientes con EA suelen presentar distinto grado de disfunción diastólica (27) que viene dada por una combinación de distintos factores entre los que cabría destacar: disminución de la complianza ventricular por la hipertrofia, alteración en la relajación miocárdica, alteraciones en la estructura del miocito (disminución del diámetro de la fibra muscular) y aumento de la fibrosis intersticial (28). La función sistólica del VI, por su parte, viene determinada por tres factores: la contracción miocárdica, la precarga y la postcarga ventricular. Así, la disfunción sistólica vendría

determinada o bien por un fallo primario de bomba (disfunción miocárdica) o bien por un desajuste entre la precarga y la postcarga (29). Como se ha comentado, el primer mecanismo compensatorio puesto en marcha ante la obstrucción a la salida del torrente sanguíneo provocada por la EA, es la hipertrofia ventricular. Cuando la hipertrofia del VI es insuficiente para mantener el gasto cardiaco, se ponen en marcha mecanismos neuroendocrinos que aumentan la precarga. Este aumento de la precarga se traducirá en un aumento en la presiones telediastólicas del VI, que de forma retrógrada puede producir aumento de la presión en la aurícula izquierda y edema pulmonar. Sólo cuando el aumento de la precarga es insuficiente se podrá objetivar una disminución significativa en la función sistólica del VI. De esta forma, los signos de insuficiencia cardiaca en los pacientes con EA pueden ser causados tanto por la disfunción sistólica como por la disfunción diastólica en presencia de FEVI normal. Ha de tenerse en cuenta que, con el envejecimiento, hay una progresiva inadaptación del gasto cardiaco a las demandas del ejercicio y una tendencia a un incremento en las presiones telediastólicas del VI. Por tanto, para un mismo AVA, la disfunción diastólica es más marcada en pacientes ancianos (30). En cualquier caso, en estadíos incipientes de EA el gasto cardiaco está preservado y es capaz de incrementar con normalidad con el ejercicio. Posteriormente, cuando la severidad de la EA progresa, el gasto permanece normal en reposo, pero es incapaz de aumentar de forma proporcional a las demandas del ejercicio. Por último, una vez que los mecanismos de compensación son insuficientes, el gasto cardiaco en reposo cae y hay un aumento en la frecuencia cardiaca. Como resultado de lo anterior, el volumen de eyección puede ser tan bajo que el gradiente transvalvular caiga a pesar de la EA severa (EA de bajo flujo y bajo gradiente)

4. DIAGNÓSTICO

4.1. EXPLORACIÓN FÍSICA

Debido a la obstrucción a la salida del torrente sanguíneo, en la EA se genera un pico sistólico tardío en el pulso carotideo, que se catalogó clásicamente como de "parvus et tardus" por tener también una amplitud reducida.

El soplo clásico de la EA es un soplo mesosistólico eyectivo, rudo, en foco aórtico irradiado a carótidas y a hueco supraclavicular. Cuando la estenosis progresa, el pico sistólico se retrasa y aumenta la intensidad, llegando a palparse thrill en algunas EA graves. La desaparición del segundo ruido como marcador de gravedad de la EA, constituye un signo muy específico pero poco sensible. Si el paciente conserva el ritmo sinusal, en ocasiones puede oírse un cuarto ruido de predominio apical, causado por la contracción auricular potente. De igual forma, en pacientes ancianos, el soplo de EA puede irradiarse a foco mitral con características piantes, constituyendo el llamado fenómeno de Gallabardin.

4.2. EXPLORACIONES COMPLEMENTARIAS

4.2.1. RADIOGRAFÍA DE TÓRAX

Los hallazgos de la radiografía de tórax, de estar presentes, suelen ser muy inespecíficos y dependen del estadio evolutivo de la enfermedad. En ocasiones puede encontrarse una silueta cardiaca de tamaño normal, con una dilatación de la porción proximal de la aorta ascendente ("dilatación postestenótica"). También puede verse un aumento de la silueta cardiaca debido a la hipertrofia o la dilatación ventricular y un crecimiento de la aurícula izquierda. Aunque actualmente existen técnicas más avanzadas para la detección de la calcificación valvular, ésta suele ser visible en muchos pacientes, siendo más evidente en la proyección lateral.

En presencia de insuficiencia cardiaca pueden verse signos de congestión pulmonar y redistribución vascular.

4.2.2. ELECTROCARDIOGRAMA

Hasta un 80% de los pacientes muestran signos electrocardiográficos de hipertrofia ventricular izquierda con o sin alteraciones de la repolarización asociadas. Otros signos inespecíficos serían datos de crecimiento auricular izquierdo, bloqueo de rama izquierda del haz de Hiss o bloqueo de rama derecha (31).

4.2.3. ECOCARDIOGRAMA TRANSTORÁCICO Y TRANSESOFÁGICO

La ecocardiografía bidimensional combinada con las técnicas doppler sigue siendo el examen de elección para el diagnóstico y la estratificación de la gravedad de la EA. Los parámetros más utilizados para la valoración de la severidad de la EA son el gradiente transaórtico medio, el área valvular (estimada por la ecuación simplificada de Bernouilli), la velocidad máxima a través de la válvula y el cociente de velocidades o de integrales de tiempo/velocidad (ITV). La **Tabla 1** resume los parámetros Doppler más importantes para el diagnóstico de EA grave (5).

	Esclerosis aórtica	**EA Leve**	**EA Moderada**	**EA Grave**
Velocidad máxima (m/s)	≤2,5 m/s	2,6-2,9	3,0-4,0	≥4,0
Gradiente Medio (mm Hg)	-	<20	20-40	≥40
AVA (cm^2)	-	>1,5	1,0-1,5	<1,0
AVA indexada (cm^2/m^2)	-	>0,85	0,60-0,85	<0,6
Relación de ITV	-	>0,50	0,25-0,50	<0,25

Tabla 1: Recomendaciones para la estratificación de la severidad de la EA.

Tanto la velocidad como el gradiente transvalvular medio son indicadores dependientes del volumen de eyección. Es poco probable que la EA sea severa si el

gradiente transaórtico es menor de 40 mm Hg y el flujo transvalvular aórtico es normal. Sin embargo, en pacientes con EA severa (AVA menor de 1 cm^2) y disfunción sistólica del VI tanto los gradientes como la velocidad pueden únicamente estar aumentados en grado leve-moderado (EA de bajo flujo y bajo gradiente). En cualquier caso, hemos de tener en cuenta que no todos los pacientes con gradiente medio<40 mm Hg, disfunción ventricular y AVA pequeña tienen EA severa, dado que algunas válvulas con estenosis moderada tienen una apertura reducida, tratándose de pacientes con cierto grado de miocardiopatía y EA moderada (EA pseudograve). En estos pacientes, la ecocardiografía de estrés con dobutamina a dosis bajas es un test diagnóstico que permite diferenciar a EA grave de pseudoestenosis aórtica (32,33). Tras la administración progresiva de dobutamina hasta dosis de 20 ug/kg/min, los pacientes con EA severa muestran incrementos en el AVA <0,2 cm^2 (con AVA <1cm^2) mientras que el gradiente medio suele aumentar por encima de 40mm Hg. En los pacientes con EA pseudosevera el AVA suele aumentar por encima de 1 cm^2 sin cambios significativos en el gradiente medio. Además, la ecocardiografía de estrés con dobutamina ayuda también a identificar la presencia de reserva contráctil o de flujo en pacientes con disfunción ventricular. Si el volumen de eyección aumenta más de un 20% se considera que el paciente tiene reserva contráctil o reserva de flujo lo cual tiene implicaciones pronósticas, puesto que la ausencia de la misma se ha asociado con un peor pronóstico tanto en pacientes sometidos a SAVR (34-36) como en aquellos que reciben tratamiento médico (35).

Con frecuencia, en estos pacientes sin reserva contráctil, la interpretación de los resultados del ecocardiograma de estrés sigue siendo difícil y en muchas ocasiones, no concluyente. Para superar estas limitaciones, se ha propuesto otro índice ecocardiográfico: el área valvular efectiva proyectada. Este índice trataría de hacer una

estimación sobre el área valvular si la tasa de flujo (volumen de eyección dividido entre tiempo de eyección) a través de la válvula fuese normal (tomando como normalidad el valor mediano de los pacientes con flujo normal: 250 ml/s) (37,38). Es cierto que, para la correcta estimación de este índice se precisa también de un incremento mínimo del 15% en la tasa de flujo. Sin embargo, a pesar de que el incremento en el volumen de eyección sea mínimo o despreciable, la tasa media de flujo transvalvular puede aumentar significativamente durante el estrés inducido por dobutamina debido a la conjunción de un aumento en la frecuencia cardiaca con una disminución en el tiempo de eyección del VI. Así, en el estudio TOPAS, en el que se analizaron los ecocardiogramas con dobutamina de 23 pacientes con EA de bajo flujo y bajo gradiente, el 51% de los pacientes no tenían reserva contráctil pero sólo un 10% de ellos mostró un incremento menor del 15% en la tasa media de flujo transvalvular (38).

En la última década se ha descrito también otro grupo de pacientes, que tendría una estenosis aórtica de bajo flujo y bajo gradiente, pero con FE conservada. Serían pues pacientes con un AVA menor de 1 cm^2, y una FEVI mayor del 60% en los que se registraría un gradiente medio <40 mm Hg y un volumen de eyección indexado <35ml/m^2. Generalmente, son pacientes ancianos, con hipertensión arterial y ventrículos hipertróficos que condicionan un volumen ventricular pequeño. Los expertos recomiendan cautela en el diagnóstico de esta entidad, siendo varias las situaciones que habrían de tenerse en cuenta antes de establecer el diagnóstico:

- Errores de medición (de entre los cuales el más común sería la infraestimación del diámetro del tracto de salida del VI) en pacientes con un AVA real mayor de 1cm^2.
- Hipertensión severa durante la realización del ecocardiograma.
- Inconsistencia entre el AVA estimada y los cocientes de velocidad o ITV.

- EA clínicamente moderada a pesar de AVA<1cm^2 en un paciente con una superficie corporal reducida.

En la estratificación de la gravedad de la EA en estos pacientes, podrían ser útiles también parámetros como el índice de pérdida de energía y la impedancia valvulo-arterial aórtica. El primero (límite de gravedad <0,52 cm^2/m^2) normaliza el AVA respecto al posible artefacto generado por el fenómeno de normalización de presiones en la aorta y ha demostrado tener valor pronóstico en pacientes con EA grave asintomática (39). La impedancia valvulo-arterial aórtica (límite de gravedad >5 mm Hg/ml/m^2) traduce la sobrecarga global que soporta el VI y ha demostrado ser predictora de aparición de síntomas y de eventos en enfermos con EA grave (40).

Todos los parámetros anteriormente mencionados son medidos, usualmente, mediante ecocardiografía transtorácica (ETT). En aquellos pacientes en los que éstos no son concluyentes, la ecocardiografía transesofágica (ETE) puede aportar una información muy valiosa. Especialmente la ETE tridimensional permite una visión anatómica muy directa de la válvula, posibilitando tanto realizar una planimetría más precisa, como identificar las áreas de calcificación y su localización.

4.2.4. TOMOGRAFÍA COMPUTERIZADA

En los casos en los que la ecocardiografía sigue arrojando dudas sobre la severidad de la EA, se ha demostrado que la cuantificación de calcio mediante TC cardiaco puede ser una herramienta útil. Así, Cueff y colaboradores establecieron en un estudio con más de 200 pacientes que un score de calcio de Agatston superior a 1650 tenía un valor predictivo positivo del 97% en el diagnóstico de EA grave (41).

Como se ha podido comprobar, son múltiples las situaciones ante las que podemos encontrarnos en pacientes con sospecha de EA grave y diversos los

parámetros diagnósticos. Para llevar a cabo un manejo integrado de los diferentes parámetros la Asociación Europea de Imagen Cardiovascular y la Sociedad Americana de Ecocardiografía han propuesto el algoritmo que se detalla en la **Figura 3** (5).

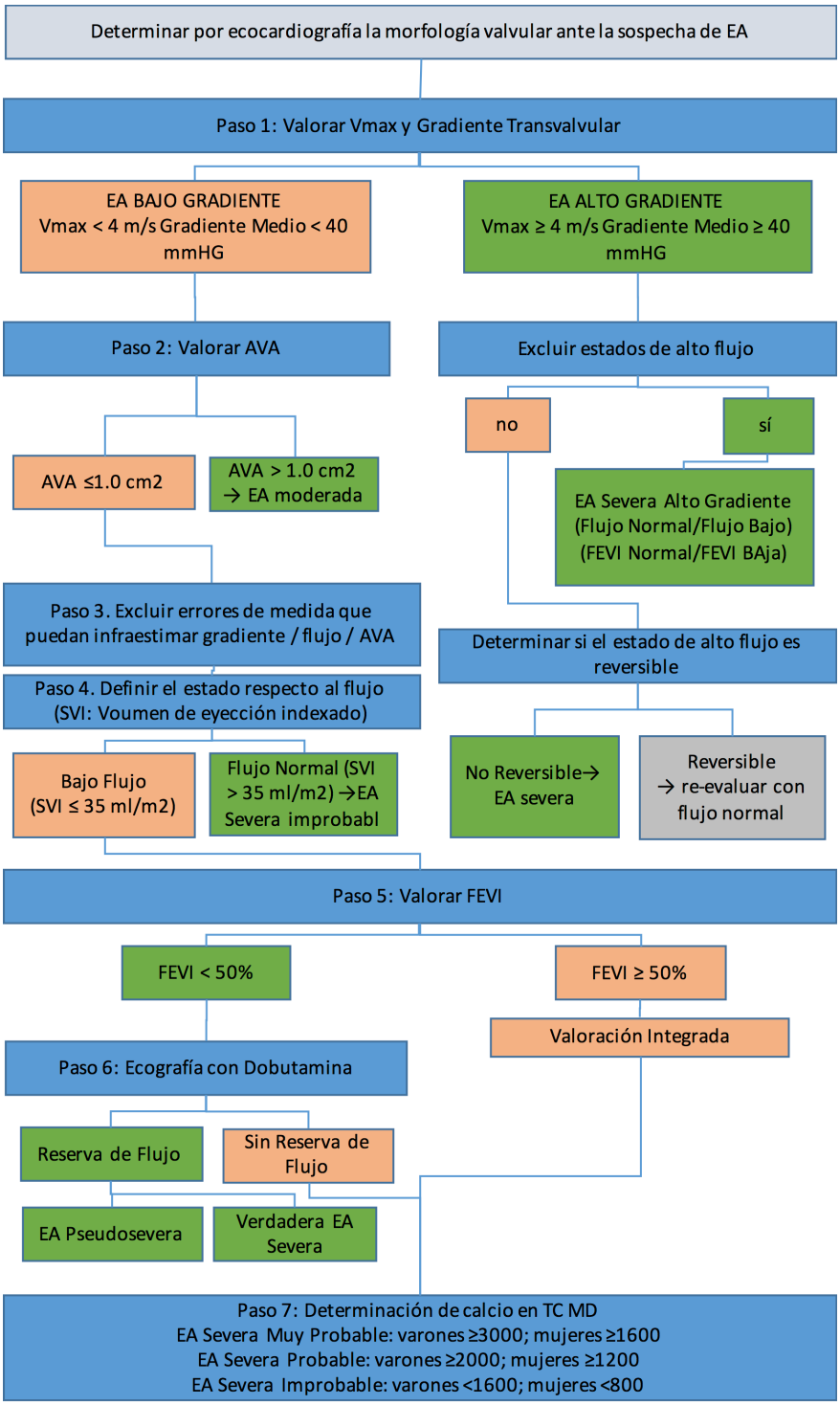

Figura 3: Algoritmo Integrado para la Determinación de la Gravedad de la Estenosis Aórtica (adaptado de Baumgartner et Al. (5). AVA: Área Valvular Aórtica; EA: Estenosis Aórtica; FEVI: Fracción Eyección Ventrículo Izquierdo; SVI: Volumen de Eyección Indexado (Stroke Volume Index); Vmax: Velocidad Máxima.

4.2.5. CATETERISMO CARDIACO

Por último, es necesario añadir que la valoración invasiva mediante cateterismo cardiaco es recomendable para determinar la severidad de la EA cuando existen discrepancias entre la clínica del paciente y los parámetros no invasivos. Con respecto al gradiente, aporta información sobre el gradiente "pico-pico" (diferencia entre la máxima presión ventricular y la máxima presión aórtica). Aunque esta medición no se corresponde con ningún parámetro fisiológico, se ha correlacionado tradicionalmente con el gradiente transvalvular medio. También puede calcularse el AVA mediante la fórmula de Gorlin usando la medida del gasto cardiaco obtenida por termodilución, o más convenientemente, por el método de Fick.

5. OPCIONES DE TRATAMIENTO

5.1. TRATAMIENTO DE LAS COMORBILIDADES

Dado que los pacientes con EA suelen tener además, otras múltiples patologías de forma concomitante, es esencial para la mejora del pronóstico, un adecuado tratamiento de las mismas. Cabe hacer especial hincapié en el tratamiento de la hipertensión arterial (HTA), puesto que en conjunción con la obstrucción valvular, contribuye a la elevación de presiones en el VI. Aunque el tratamiento óptimo de pacientes con EA e HTA aún no ha sido bien establecido, clásicamente se ha recomendado el uso de inhibidores de la enzima convertidora de angiotensina por su acción beneficiosa sobre la fibrosis ventricular. En pacientes con enfermedad coronaria concomitante, los betabloqueantes serían el fármaco de elección (42,43). En cualquier caso, la escalada de dosis o la adición de nuevos fármacos ha de ser progresiva hasta controlar las cifras de tensión arterial. Se recomienda evitar el tratamiento con

diuréticos, especialmente en pacientes con cavidad ventricular reducida, puesto que su uso podría desencadenar síntomas de bajo gasto.

5.2. INDICACIÓN DE LA INTERVENCIÓN

Según las guías de práctica clínica, se recomienda intervenir a aquellos pacientes que presenten síntomas secundarios a EA severa en sus actividades habituales o en un test de esfuerzo (Clase I) (44,45). La intervención también estaría recomendada (Clase I) en pacientes asintomáticos con EA severa y disfunción ventricular (FEVI< 50%). En pacientes con EA que precisan cirugía cardiaca por otra patología (cirugía de revascularización coronaria, aneurisma aórtico, intervención sobre otra valvulopatía), las guías de práctica clínica europeas y americanas recomiendan la intervención con indicación clase I para los casos de EA severa y con indicación clase IIa para los casos de EA moderada. En los pacientes sintomáticos con EA de bajo flujo y bajo gradiente, el nivel de recomendación dependería de la presencia o no de reserva contráctil en el ecocardiograma de estrés con dobutamina. Así, en pacientes con reserva contráctil la indicación sería clase IIa, mientras que en los pacientes que carecen de ella la indicación sería IIb, en base a que su eficacia está menos probada.

De igual forma, la intervención también estaría recomendada en pacientes asintomáticos con caída de presión en la prueba de esfuerzo o con EA muy grave y bajo riesgo quirúrgico definido como una puntuación menor de 4 en la escala de riesgo de la Society of Thoracic Surgeons (clase IIa). A este respecto, la guía de la Sociedad Europea de Cardiología estima que la EA es muy grave cuando la velocidad transvalvular máxima es mayor de 5,5 m/s (44); por su parte, las guías de la American Heart Association/American College of Cardiology consideran que la EA es muy grave en los casos en los que la velocidad transvalvular máxima es mayor de 5 m/s.

El tratamiento de los pacientes sintomáticos con EA de bajo flujo, bajo gradiente y fracción de eyección preservada, aún es controvertido. En este complejo grupo de pacientes, la indicación de la intervención debe establecerse tras valorar conjuntamente múltiples variables entre las que estarían el riesgo quirúrgico, los síntomas y los resultados de varias exploraciones complementarias (Clase IIa).

Con respecto a la progresión de la enfermedad, en pacientes asintomáticos con EA severa, las guías americanas recomiendan la intervención con indicación clase IIb en casos de pacientes de bajo riesgo con rápida progresión; y las guías europeas, con indicación clase IIa cuando exista calcificación severa y la tasa de progresión de la velocidad transvalvular máxima sea ≥0,3m/s/año.

Por último, las guías europeas recomiendan la intervención con indicación clase IIb en pacientes asintomáticos con riesgo bajo y FEVI normal si cumplen alguno de los tres siguientes criterios: 1) elevación significativa y repetida de péptidos natriuréticos, en ausencia de otra explicación para la misma; 2) incremento del gradiente medio con el ejercicio >20 mm Hg; 3) excesiva hipertrofia del VI en ausencia de HTA.

5.3. OPCIONES DE TRATAMIENTO

5.3.1. VALVULOPLASTIA AÓRTICA PERCUTÁNEA

La valvuloplastia aórtica percutánea se consideró tradicionalmente una opción terapéutica para aquellos pacientes con EA severa que no podían ser operados o como terapia puente a la cirugía en pacientes considerados hemodinámicamente inestables (46). Si bien es un procedimiento con una incidencia de complicaciones relativamente baja en la actualidad, la tasa de reestenosis es alta y su utilidad a medio y largo plazo es muy dudosa. Actualmente su uso se encuentra vinculado, mayoritariamente, a los procedimientos de sustitución transcatéter de válvula aórtica (TAVR), dentro del

procedimiento previo al implante de válvula y, en menos casos, como puente al mismo en pacientes inestables.

5.3.2. SUSTITUCIÓN QUIRÚRGICA DE VÁLVULA AÓRTICA

La sustitución quirúrgica de la válvula aórtica (SAVR) es la cirugía valvular cardiaca más frecuente, de la cual se realizan >200.000 procedimientos cada año. Diversas series han demostrado que tiene un efecto beneficioso sobre la supervivencia, los síntomas y la función del VI en pacientes con EA grave sintomática (47,48). Se estima que el SAVR se asocia a una mortalidad del 1-3% en pacientes menores de 70 años y del 4-8% en pacientes mayores seleccionados (44). En cualquier caso, pese al mal pronóstico de los pacientes no intervenidos y a que la edad en sí no se considera una contraindicación para la cirugía, los registros muestran que aproximadamente un tercio de los pacientes con indicación de intervención no son remitidos a cirugía (49). Esta fue una de las principales causas que llevaron al desarrollo de técnicas menos invasivas para el tratamiento de la EA grave sintomática.

5.3.3. SUSTITUCIÓN TRANSCATÉTER DE VÁLVULA AÓRTICA

Así pues, la sustitución quirúrgica de la válvula aórtica era hasta 2002, el único tratamiento eficaz a largo plazo de la EA sintomática. En ese año, siguiendo trabajos experimentales realizados en la década de los 90 (50), el Dr. Alain Cribier llevó a cabo el primer caso de implante transcatéter de válvula aórtica (TAVR) (51). Desde entonces, esta intervención ha seguido un desarrollo técnico exponencial y se ha consolidado como una opción de tratamiento para un grupo cada vez más numeroso de pacientes (52). Así, a la primera experiencia en humanos anteriormente citada siguieron una serie de registros uni y multicéntricos que confirmaron el TAVR como una técnica factible y como una opción de tratamiento prometedora para pacientes inoperables o de muy alto riesgo quirúrgico (53-60). Posteriormente, tras la publicación del estudio prospectivo y

aleatorizado PARTNER (Placement of Aortic Transcatheter Valves)(61,62), las guías de práctica clínica americanas y europeas establecieron que el TAVR era una alternativa válida al SAVR en pacientes considerados inoperables o de muy alto riesgo. La **Tabla 2** resume las indicaciones para el implante transcatéter de válvula aórtica según la guía de la Sociedad Europea de Cardiología publicadas en 2012 (44).

Recomendación	**Clase**	**Nivel**
Sólo debe realizarse el TAVR en hospitales con Cirugía Cardiaca en el centro	I	C
Sólo debe realizarse el TAVR con un equipo cardiológico multidisciplinar que incluya cardiólogos, cirujanos cardiacos y otros especialistas si es necesario.	I	C
El TAVR está indicado en pacientes que no son candidatos a cirugía, cuando existe una expectativa de mejoría de sus síntomas y una esperanza de vida>12 meses.	I	B
Se puede considerar en TAVR en pacientes de alto riesgo quirúrgico que pueden ser operados pero en los que el equipo cardiológico prefiere el TAVR tras valorar las características y comorbilidades individuales del paciente.	IIa	B

Tabla 2: Indicaciones de TAVR según la Sociedad Europea de Cardiología.

Sin embargo, hemos de tener en cuenta que desde 2012 han surgido múltiples estudios evaluando el TAVR en pacientes de menor riesgo quirúrgico (63-65). Por ello, la American Heart Association y el American College of Cardiology han publicado en marzo de 2017 una actualización de las guías de práctica clínica que contemplan los últimos estudios de TAVR en pacientes de riesgo intermedio(66). Así, las indicaciones en función del riesgo estimado (**Tabla 3**), quedarían del siguiente modo:

- En pacientes en los que se considera un procedimiento de TAVR o en los que la cirugía se considera de alto riesgo, un equipo cardiológico multidisciplinar ("Heart Team") compuesto por diferentes expertos en valvulopatías (cardiólogos intervencionistas, cirujanos cardiacos, anestesistas, cardiólogos especialistas en

imagen cardiovascular) debe colaborar para proporcionar el tratamiento óptimo al paciente (Clase IC).

- En pacientes en los que el riesgo quirúrgico se considera "prohibitivo" o inasumible, se recomienda llevar a cabo un procedimiento de TAVR si se considera que el paciente tiene una expectativa de vida mayor de 12 meses (Clase I-A). Se considera que un paciente tiene un riesgo quirúrgico prohibitivo si el riesgo de complicación mayor tras la cirugía es igual o superior al 30% en los primeros 30 días, si presenta comorbilidades que afecten al menos a 3 sistemas vitales (sin expectativa de mejoría tras la cirugía) o si presenta características anatómicas que impiden o incrementan el riesgo de la intervención quirúrgica (aorta de porcelana, radioterapia torácica previa, bypass arterial adherido a la pared torácica). Con respecto a ediciones anteriores de guías de práctica clínica, el nivel de evidencia pasa de B a A en base a la publicación de seguimientos a largo plazo de estudios aleatorizados y de nuevos estudios observacionales (67,68).
- Un procedimiento de TAVR no estaría indicado en pacientes cuyas comorbilidades pueden anular el beneficio esperado tras la corrección de la EA. (Clase III-B)
- En pacientes de alto riesgo quirúrgico, la elección entre un procedimiento de TAVR o de SAVR debe hacerse en función de las características, comorbilidades y preferencias del paciente (Clase I-A). En este grupo de pacientes, el TAVR se equipara a la SAVR en base a los resultados del estudio PARTNER (69) y de múltiples registros multicéntricos(60,68,70).
- Se recomienda la sustitución quirúrgica de válvula aórtica en pacientes con EA severa sintomática (y en aquellos asintomáticos que tienen indicación de

intervención) que presentan un riesgo quirúrgico bajo o intermedio (Clase I-B). En este grupo de pacientes, el TAVR se considera una alternativa razonable a la cirugía dependiendo de los riesgos específicos de cada paciente, sus características y preferencias (Clase IIa-B). En el estudio PARTNER II en el que se incluyeron pacientes sintomáticos con EA severa y score de riesgo STS ≥ 4 no hubo diferencias entre TAVR y SAVR en la incidencia de muerte o accidente cerebrovascular incapacitante durante los dos primeros años tras la intervención (HR: 0,89; IC del 95%: 0,73 a 1,09; p = 0,25)(64). La mortalidad por cualquier causa fue del 16,7% de los pacientes aleatorizados a TAVR y del 18% de los aleatorizados a SAVR. La incidencia de accidente cerebrovascular incapacitante fue similar en ambos grupos (6,2% TAVR Vs 6,3% SAVR). En un propensity matched score que comparó pacientes tratados con la válvula Sapiens 3 y pacientes del grupo quirúrgico del estudio PARTNER 2, el tratamiento transcatéter fue no inferior y superior al tratamiento quirúrgico (-9,2%; IC del 95%: -13,0 a -5,4; P <0,0001)(71). Aunque no está contemplado en las guías de la AHA, recientemente se presentaron los resultados del estudio SURTAVI(65). Este estudio confirmó la no-inferioridad de TAVR con prótesis autoexpandible Vs cirugía en pacientes con riesgo quirúrgico intermedio (STS promedio 4,5±1,6%). En un seguimiento a dos años la incidencia de muerte o ACV incapacitante fue del 12,6% en el grupo de TAVR Vs 14% en los pacientes tratados quirúrgicamente (p no inferioridad >0,999). La cirugía se asoció a mayor incidencia de insuficiencia renal , fibrilación auricular y necesidad de transfusión mientras que el TAVR presentó mayores tasas de insuficiencia aórtica residual y necesidad de implante de marcapasos.

- La valvuloplastia percutánea con balón puede ser considerada como puente a un procedimiento de TAVR o SARV en pacientes con EA sintomática (Clase IIb-C).

CATEGORÍA DE RIESGO	CRITERIOS
BAJO	• STS-PROM <4% y • Ausencia de fragilidad y • Ausencia de comorbilidad y • Ausencia de problemas específicos del procedimiento
INTERMEDIO	• STS-PROM 4%-8% ó • Fragilidad leve ó • Comorbilidad que afecta a un sistema orgánico mayor (no se espera que mejore tras el procedimiento) ó • Un posible problema específico del procedimiento.
ALTO	• STS-PROM >8% ó • Fragilidad moderada a severa ó • Comorbilidad que afecta a 2 sistemas orgánicos mayores (no se espera que mejoren tras el procedimiento) ó • Un posible problema específico del procedimiento.
PROHIBITIVO	• PROMM >50% a un año ó • Fragilidad severa ó • Comorbilidad que afecta a ≥3 sistemas orgánicos mayores (no se espera que mejoren tras el procedimiento) ó • Problemas específicos del procedimiento.

Tabla 3: Categorías de riesgo en función de las características del paciente. STA PROM: riesgo predicho de mortalidad. PROMM:riesgo predicho de mortalidad o morbilidad mayor. (Adaptado de Otto et Al (72)

Como se ha comentado, las recomendaciones de la Sociedad Europea de Cardiología datan de 2012, se espera que próximamente sean actualizadas para recoger las conclusiones derivadas de los estudios anteriormente mencionados.

II. SUSTITUCIÓN TRANSCATÉTER DE VÁLVULA AÓRTICA

1. DIFERENTES VÁLVULAS DE IMPLANTE TRANSCATÉTER

Como se ha comentado, el TAVR es una técnica que ha sufrido una expansión exponencial en los últimos 15 años, lo cual se ha traducido en el desarrollo rápido de diferentes tipos y tamaños de válvulas aórticas de implante transcatéter. En la actualidad son varios los dispositivos que han obtenido la aprobación de la Comunidad Europea entre los cuales cabe citar: la válvula balón-expandible SAPIEN de Edwards (Edwards SAPIEN, Edwards Lifesciences, Irvine, CA, EE.UU), la válvula auto-expandible CoreValve (Medtronic, Inc., Minneapolis, MN, EE.UU), la válvula autoexpandible de Portico (St Jude Medical, St Paul, MN, EE.UU), la prótesis Direct Flow (Direct Flow Medical, Inc., Santa Rosa, CA, EE.UU), la válvula Lotus (Boston Scientific Corporation, Natick, MA, EE.UU), la prótesis Symetic Acurate (Symetis SA, Ecublens, Suiza), la válvula JenaValve (JenaValve, Munich, Alemania) y la prótesis Medtronic Engager (Medtronic, Inc., Minneapolis, MN, EE.UU)(73).

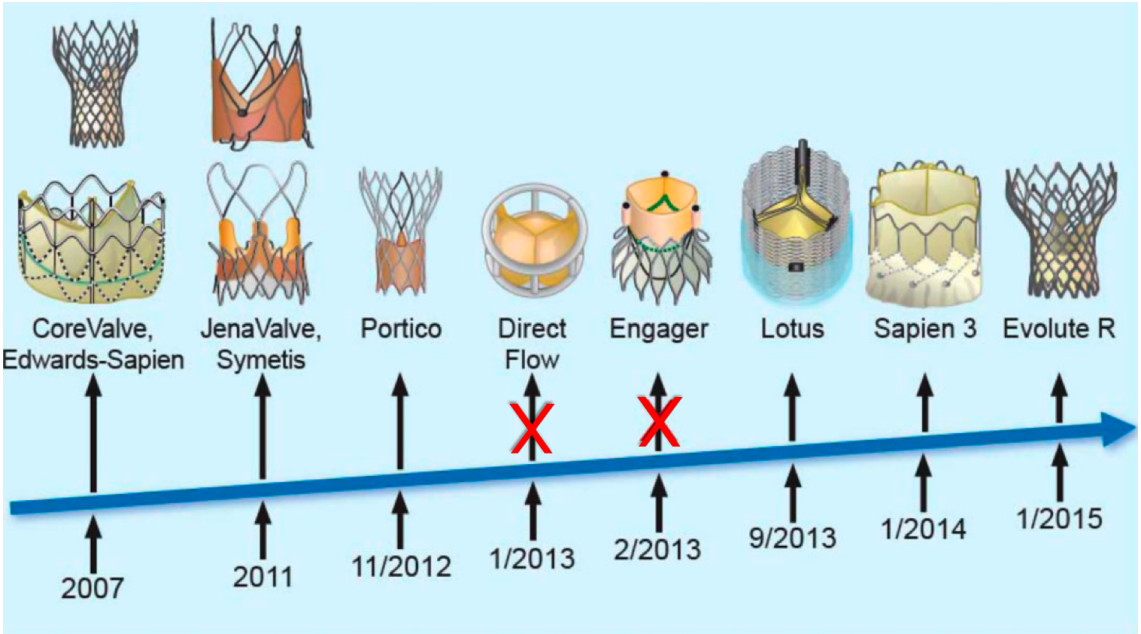

Figura 4: Bioprótesis Aórticas de Implante Transcatéter con Marca CE (Adaptado de Figulla et Al (73))

De entre todos los dispositivos anteriormente mencionados, las dos válvulas que han demostrado su eficacia en un mayor número de registros y estudios aleatorizados son la familia de válvulas balón-expandibles Edwards y la familia de válvula autoexpandibles CoreValve, cuyas características principales veremos a continuación.

1.1. VÁLVULAS BALÓN-EXPANDIBLE EDWARDS

Las dos primeras generaciones de la válvula Edwards (Cribier-Edwards y Edwards Sapien; Edwards Lifesciences, Irvine CA, EE.UU) constaban de tres valvas de pericardio bovino montadas sobre un stent de acero inoxidable. Para su implante era preciso un catéter de liberación de 22 a 24F de diámetro. La válvula Sapien XT constituyó la tercera generación de esta prótesis e incorporó una serie de cambios en el stent, que pasó a ser de cromo-cobalto y a tener una configuración diferente de los struts. Estas modificaciones permitieron reducir el tamaño de la válvula sin una pérdida en la fuerza radial. Esto se tradujo en una disminución del tamaño de los catéteres de liberación y de los introductores arteriales. Así pues, gracias al introductor expandible eSHEAT las válvulas de 20 y 23 mm precisaban un introductor de 16F, la de 26mm de 18F y la de 29mm de 19F (74). La última generación de esta familia de prótesis es la válvula Sapien 3. En comparación con las versiones anteriores, la principal modificación es la incorporación de una "falda" de polietileno en el borde exterior y ventricular del stent (75). Esta implementación mejora el sellado de la válvula en el anillo aórtico y ha reducido de forma significativa la incidencia de insuficiencia aórtica (IAo) residual postprocedimiento (76). Los tamaños disponibles de la válvula Sapien 3 son 23 y 26 mm que precisan un introductor expandible de 14F y 29 mm que requiere un introductor de 16F.

1.2. VÁLVULA AUTOEXPANDIBLE COREVALVE

La primera generación de la válvula CoreValve (Medtronic, Inc., Minneapolis, MN, EE.UU) estaba compuesta por un stent autoexpandible con una válvula de pericardio bovino en el interior que precisaba de un catéter de liberación de 25F. La segunda generación constaba de 3 valvas de pericardio porcino situados más cranealmente en el stent para lograr un posicionamiento supraanular de los velos. Además, se rediseñó el stent para otorgarle una mayor fuerza radial y permitir su climpaje en un catéter de liberación de 21F. La tercera generación incorporó tejido de sellado en la porción ventricular para permitir una mejor adaptación anatómica de la válvula. Este dispositivo estaba disponible en 23, 26, 29 y 31 mm y precisaban un catéter de 18F para su liberación (74).

La última generación de esta familia de dispositivos es la válvula CoreValve Evolut R que introduce tres modificaciones sustanciales respecto a sus predecesoras(77):

- Un tratamiento anti-mineralización de los velos de pericardio porcino con ácido alfa-amino-oleico.
- Una geometría rediseñada de las celdas del stent que permiten un mejor climpaje en el catéter de liberación y que otorgan al sistema una menor pero constante fuerza radial, lo cual permite una mejor adaptación anatómica al anillo aórtico.
- Un sistema de liberación ha sido rediseñado que presenta un menor perfil (reduciendo el tamaño del introductor a 14F), permite un posicionamiento más preciso y posibilita que la válvula sea totalmente recapturable incluso cuando se ha liberado un 80% de la superficie del stent.

2. ESTUDIO PREPROCEDIMIENTO

2.1. SELECCIÓN DEL TAMAÑO DE LA PRÓTESIS

Una adecuada medición del tamaño del anillo aórtico es fundamental para la selección del tamaño de la prótesis. Dada la naturaleza elíptica del anillo, las técnicas tridimensionales como el TC multicorte (TC MC) o la ecografía transesofágica 3D se consideran más adecuadas que las técnicas bidimensionales (ecocardiografía bidimensional y angiografía) (78). Así, seleccionar el tamaño de la prótesis basándose sólo en el diámetro mínimo o máximo podría dar lugar a infraestimar o sobrestimar, respectivamente, el tamaño de la misma. Infraestimar el tamaño de la prótesis necesaria podría dar lugar a la migración de la misma o a la ocurrencia de un grado significativo de IAo post-procedimiento. Por otra parte, sobreestimar el tamaño aumenta significativamente el riesgo de ruptura del anillo. Para reducir la ocurrencia de estas complicaciones, varios estudios recomiendan usar el perímetro o el área del anillo aórtico medido por una técnica tridimensional para seleccionar el tamaño adecuado de la prótesis. En la práctica clínica actual el TC MC se ha convertido en la técnica de elección dada su adecuada resolución espacial y la posibilidad de postprocesamiento con software específico para TAVR (79).

Para las prótesis SAPIEN, se recomienda entre un 5% y un 10% de sobredimensión del tamaño de la prótesis (área nominal de la prótesis/área del anillo medida por TC multicorte). Si la válvula seleccionada sobredimensiona más del 15-20% el área del anillo, se recomienda liberarla hinchando el balón con un 10% menos del volumen nominal para minimizar el riesgo de ruptura del anillo (80). A este respecto, en los casos limítrofes entre uno y otro tamaño de prótesis, la tendencia actual con la válvula Sapien 3 se dirige más a una expansión completa del dispositivo de menor tamaño en detrimento de implante de prótesis mayores con hinchado por debajo del volumen nominal (81). En cualquier caso, hemos de tener en cuenta que

sobredimensionar el tamaño de la prótesis en base a las mediciones del área no es equivalente a sobredimensionarla en base a las mediciones del perímetro. Así, sobredimensionar un 10-20% en base al perímetro, equivaldría a sobredimensionar un 30-40% en base al área, aumentando, por tanto el riesgo de complicaciones mecánicas en la raíz aórtica (82).

2.2. VALORACIÓN Y TRATAMIENTO DE LA ENFERMEDAD CORONARIA

La enfermedad coronaria es muy prevalente entre los pacientes con EA severa degenerativa. Así, se ha descrito la presencia de enfermedad coronaria en casi el 60% de los pacientes sometidos a SARV (83). De acuerdo con las guías de práctica clínica americanas y europeas, se recomienda la realización de una coronariografía a todos los pacientes en los que se considera la realización de un procedimiento de TAVR (44,45). Varios estudios observacionales han demostrado que la angioplastia coronaria en pacientes seleccionados para TAVR es factible y no añade riesgo en términos de mortalidad, infarto de miocardio o ACV (84). Pese a ello, el beneficio a largo plazo del tratamiento de la enfermedad coronaria en pacientes que van a ser sometidos a TAVR aún no ha sido bien establecido (85).

2.3. ELECCIÓN DEL ACCESO VASCULAR

Se recomienda la valoración del calibre y tortuosidad del eje femoro-ilíaco por angiografía o preferentemente, por TC MC. Si el calibre arterial a este nivel es adecuado (>5-6 mm con las nuevas generaciones de válvulas), la vía transfemoral es la vía de acceso recomendada.

2.3.1. ACCESO TRANSFEMORAL

Como se ha comentado, cuando es posible, el acceso trasnfemoral es considerado el acceso por defecto en TAVR (86-88). Aunque inicialmente se realizaba

disección quirúrgica de la arteria femoral, pronto las nuevas generaciones de válvula que precisaban introductores de menor calibre, y el desarrollo de dispositivos de cierre arterial, permitieron llevar a cabo procedimientos totalmente percutáneos. El acceso transfemoral se ha asociado con un mejor pronóstico en términos de mortalidad (89) y de daño miocárdico que otros accesos (90).

2.3.2. ACCESO TRANSAPICAL

El acceso transapical fue el que se utilizó inicialmente en aquellos pacientes en los que el acceso transfemoral no era posible. Aunque permite un estrecho control de la válvula durante la liberación de la misma, actualmente su uso está en descenso dado su carácter más invasivo (lo cual se traduce en mayor daño miocárdico y recuperación más dificultosa) y la necesidad de minitoracotomía. Además, es un acceso que no estaría indicado en pacientes con enfermedad pulmonar severa, deformidad torácica, disfunción ventricular severa o en los que se ha documentado la presencia de trombo intraventricular.

2.3.3. ACCESO TRANSAÓRTICO

Aunque inicialmente fue un acceso que se utilizaba únicamente cuando los abordajes transfemoral y transapical no eran posibles, en los últimos años ha sido cada vez más usado. La realización de un exhaustivo análisis de la aorta ascendente mediante TC multicorte es esencial cuando se contempla este abordaje. Así, la zona de punción en la aorta debe estar libre de calcio y situarse a una distancia mínima de 6-7 cm del anillo valvular (91). Aunque la calcificación de la aorta ascendente es frecuente, en la mayoría de los pacientes, tiene un carácter parcheado, siendo poco habituales los casos de una auténtica “aorta de porcelana”. En comparación con el abordaje transapical, el acceso transaórtico evita el daño ventricular en el ápex, tiene menor inferencia con la dinámica respiratoria y menor incidencia de retracción costal y de derrame pleural.

2.3.4. OTROS ACCESOS

Los accesos transsubclavio o transaxilar se han considerado como alternativas en pacientes con enfermedad arterial periférica severa (92,93). En general, se prefiere un abordaje desde el lado izquierdo puesto que otorga un mejor ángulo para el despliegue de la válvula. Sólo en aortas muy verticales se preferiría un acceso desde la sublaclavia derecha. Por supuesto, es precisa una evaluación meticulosa preprocedimiento que descarte la existencia de tortuosidad o estenosis significativas (94). También ha de tenerse en cuenta que en pacientes con bypass previo de arteria mamaria izquierda, la inserción del introductor podría dar lugar a isquemia miocárdica. Por último, recientemente se han publicado registros que muestran que el acceso transcarotídeo es factible, seguro y no se asocia a una mayor tasa de ACV (95,96).

3. RESULTADOS DEL PROCEDIMIENTO

Diferentes estudios aleatorizados, registros y metaanálisis han mostrado tasas de éxito del procedimiento superiores al 90% (88).

Con respecto a la mortalidad, cabe señalar que los primeros estudios de TAVR se hicieron en pacientes considerados de muy alto riesgo (Cohorte A) o inoperables (Cohorte B). Además, se ha demostrado que las tasas de mortalidad da corto plazo suelen ser inferiores en los estudios clínicos aleatorizados que en los registros uni o multicéntricos(97). Así, en el estudio PARTNER los pacientes tenían un STS medio del 11% y una edad media de 83 años(61,62). La mortalidad a los 30 días fue del 3,4% y del 5% en las cohortes A y B, respectivamente. La supervivencia al año en la cohorte A fue del 76% y del 69,3% en la cohorte B. En un metaanálisis que estudió a 8268 pacientes incluidos en diversos registros entre 2007 y 2010 (STS score >8%; EuroSCORE >20%) la mortalidad a los 30 días fue del 9,2% y la mortalidad al año fue

del 20,8% y 32,2% en los grupos de acceso transfemoral y transapical, respectivamente(97).

Posteriormente, el perfil de riesgo de los pacientes fue disminuyendo, reduciéndose también las tasas de mortalidad a corto y medio plazo. Así, los pacientes incluidos en el estudio PIVOTAL que se realizó con la valvula CoreValve tenían un riesgo STS de 7,4% siendo la mortalidad al año del 13.9% (98). El estudio NOTION fue el primero que incluyó pacientes con EA severa independientemente de su score de riesgo (63). En dicho estudio, el STS promedio fue de 2,9% y la mortalidad fue del 2,1% y el 4,9% a los 30 días y al año, respectivamente. Por último, entre los estudios recientemente publicados en pacientes de riesgo intermedio, el estudio PARTNER 2 evidenció una mortalidad del 3,9% a los 30 días y del 12,3% al año entre pacientes con un STS promedio de 5,8%(64). De igual forma, en el recientemente publicado estudio SURTAVI (STS medio 4,4%), la mortalidad a los 30 días, 12 meses y 24 meses fue del 2,2%, 6,7% y 11,0%, respectivamente (65).

En términos de clase funcional, el TAVR se ha asociado a mejorías en la clase funcional de la NYHA, en el test de la marcha de 6 minutos y en diversos cuestionarios estandarizados que evalúan la calidad de vida (Short Form (SF)-12, SF-36, Kansas City Cardiomyopathy Questionnaire, EuroQuol-5D, y Duke Activity Status Index) (99-105).

4. COMPLICACIONES DEL PROCEDIMIENTO

En los primeros estudios, la descripción de las complicaciones tras el procedimiento de TAVR variaba en función de las definiciones de las mismas utilizadas por cada investigador. A este respecto, el documento de consenso “Valve Academic Research Consortium” (VARC) actualizado en 2012, supuso un gran avance al proporcionar una definición estándar de las complicaciones específicas (106).

Seguidamente, haremos referencia a las principales complicaciones descritas tras un procedimiento de TAVR.

4.1. COMPLICACIONES DEL ACCESO VASCULAR

4.1.1. COMPLICACIONES EN EL ACCESO TRANSFEMORAL

Pese a que el tamaño de los introductores se ha reducido desde los 24-26 F de los primeros dispositivos hasta los 14-16F de los actuales, hoy en día, las complicaciones vasculares se siguen produciendo hasta en un 16% de los procedimientos (107,108). A grandes rasgos, estas complicaciones pueden dividirse en complicaciones hemorrágicas y disecciones o oclusiones vasculares tras la retirada del introductor. Se han identificado varios factores de riesgo que aumentan el riesgo de complicaciones vasculares, entre los que cabe destacar: la proporción entre el tamaño del introductor y la luz arterial, la calcificación circunferencial y la tortuosidad del vaso. Es importante tener en cuenta estos factores en la planificación del procedimiento, ya que las complicaciones vasculares han demostrado ser un importante predictor de la mortalidad a 30 días (109). La mayoría de los sangrados intraprocedimiento se deben al fallo de los sistemas de cierre (los más comúnmente usados son el ProStarXL y el Perclose Proglide, ambos de Abbott Vascular, Abbott Park, Illinois, USA) y pueden ser resueltos de forma percutánea. A este respecto, es importante asegurar en todo momento el acceso a la femoral terapéutica, que suele hacerse mediante acceso retrógrado desde la otra arteria femoral. De esa forma, puede hincharse un balón para realizar hemostasia o implantar un stent cubierto.

4.1.2. COMPLICACIONES DEL ACCESO TRANSAPICAL

Aunque las complicaciones graves del acceso transapical son infrecuentes (110), la necesidad de minitoracomía puede provocar sangrado de los vasos intercostales o por la fractura costal, especialmente en pacientes tratados con doble antiagregación. Esto se

traduce en una mayor necesidad de transfusión que el resto de los accesos intravasculares (necesidad de transfusión de >2 concentrados en acceso transapical 25,4% Vs 11,5% en accesos transvasculares)(108).

Cuando se produce un desgarro del ápex, sobre todo en pacientes con miocardio friable o hipertrófico, suele ser necesaria la conversión a cirugía abierta con circulación extracorpórea. Para reducir el trauma quirúrgico, se están desarrollando retractores de tejido no metálicos así como sistemas de cierre del acceso transapical (111).

4.2. TAPONAMIENTO CARDIACO

La incidencia de taponamiento cardiaco durante un procedimiento de TAVR varía entre el 0,2 y el 4,3%(108). Tres son los mecanismos fisiopatológicos principales por los que puede producirse:

- Disección o rotura del anillo durante la valvuloplastia con balón o la liberación de la válvula. Como se ha comentado previamente, una adecuada selección del tamaño valvular es indispensable para evitar esta complicación.
- Perforación del ventrículo derecho por el cable de marcapasos. A este respecto, se recomienda la colocación bajo fluoroscopia del marcapasos transitorio, así como el empleo de cables de marcapasos provistos de balón en su extremo distal.
- Perforación del VI causada por la guía de alto soporte. Para evitar esta complicación se han desarrollados guías preformadas y se recomienda un cuidadoso intercambio de la guía con la que se pasa al VI por la guía de alto soporte con ayuda de un catéter Amplatzer.

La ocurrencia de taponamiento cardiaco puede ser sospechada cuando se produce una caída brusca de la presión arterial y ha de confirmarse rápidamente mediante ecocardiografía intraoperatoria. Resulta de vital importancia identificar la causa del

taponamiento, ya que mientras las perforaciones de VD pueden ser resueltas mediante fluidoterapia y pericardiocentesis, la perforación del VI o la rotura aórtica suelen requerir intervención quirúrgica urgente.

4.3. ROTURA DE LA RAÍZ AÓRTICA AÓRTICA

Tanto la rotura de la raíz aórtica como el hematoma periaórtico son complicaciones infrecuentes descritas, aproximadamente, en <1% de los procedimientos de TAVR (107) pero con una elevada mortalidad asociada (50%) (112). La disección o la rotura pueden producirse tanto a nivel del anillo como del tracto de salida del VI y pueden desencadenarse durante la predilatación, implante de la válvula o postdilatación de la misma. El uso de prótesis balón-expandibles, la excesiva sobredimensión de la prótesis respecto al tamaño del anillo y la calcificación en el tracto de salida del VI, se han asociado significativamente con una mayor incidencia de esta complicación (112). La rotura no contenida de la raíz aórtica precisa cirugía urgente y suele requerir la retirada de la prótesis implantada transcatéter y la reparación o sustitución de la raíz aórtica.

4.4. OBSTRUCCIÓN CORONARIA

Esta complicación tiene una incidencia estimada entre el 0,2 y 0,4% (108,113) y suele estar causada por fragmentos de los velos de la válvula nativa que se desplazan y ocluyen algunos de dos óstiums coronarios. Ha de tenerse en cuenta que en pacientes con antecedentes de SARV previo que se someten a TAVR (procedimientos "*valve in valve*") esta complicación es más frecuente y puede producirse hasta en el 2,5-3,5% de los casos (113,114). Además de este factor, también se ha asociado con una mayor incidencia de obstrucción coronaria el sexo femenino, el uso de una prótesis balón-expandible, una configuración "tubular" de la aorta (diámetro de los senos de Valsalva

<30mmm) y una implantación baja del ostium de las coronarias (<12 mm desde el plano valvular).

Varias estrategias se han propuesto para intentar prevenir o prever esta complicación, entre las que estaría realizar un aortograma en proyección oblicua anterior izquierda craneal durante la valvuloplastia con balón o utilizar una prótesis autoexpandible y recapturable que pudiese ser retirada si durante el despliegue de la misma se observan signos de posible obstrucción coronaria. Otros grupos prefieren, en pacientes identificados de alto riesgo para oclusión coronaria, realizar el implante de la prótesis con una guía de angioplastia situada en la arteria descendente anterior y un balón de angioplastia o stent emplazado sin desplegar en ella. Esta estrategia permite un rápido tratamiento de la obstrucción coronaria, si bien su efecto en términos de reducción de la mortalidad aún no ha sido probado.

4.5. INSUFICIENCIA RENAL

La insuficiencia renal post-TAVR tiene una incidencia estimada en torno al 24% (115,116) y ha mostrado ser un predictor independiente de mortalidad tanto a 30 días como al año (116,117). La etiología de la IR en estos pacientes es multifactorial: en muchos de estos pacientes es una comorbilidad previa, además, algunos de los exámenes que se realizan pre-TAVR pueden empeorar la función renal (coronariografía, TC), por último, los episodios de hipotensión que pueden desencadenarse durante el procedimiento o la necesidad de transfusiones pueden agravar el deterioro. A pesar de que los procedimientos transapicales suelen requerir menos contraste, la incidencia de IR es menor en los pacientes tratados mediante acceso transfemoral, lo que puede explicarse por una menor necesidad de transfusión en estos enfermos. Se han propuesto protocolos de TC pre-TAVI con uso de menor cantidad de contraste para intentar evitar esta complicación.

4.6. EVENTOS CEREBROVASCULARES

Según los datos de un metaanálisis con más de 10.000 pacientes, la incidencia de ACV/AIT en los 30 días posteriores a un procedimiento de TAVR se estima en torno al 3,3 ± 1,8%, asociándose a mayor mortalidad a corto y medio plazo (118). Aunque el estudio PARTNER mostró mayor incidencia de ACV en pacientes tratados con TAVR que en pacientes sometidos a SAVR (61,62), los datos del registro GARY muestran que el TAVR no es inferior al SAVR en términos de ocurrencia de ACV o AIT (108). Los factores asociados con una mayor incidencia de ACV en los 30 días posteriores a un procedimiento de TAVR son: el sexo femenino, la insuficiencia renal crónica, la fibrilación auricular de nueva aparición y el hecho de que le centro se encuentre al inicio de su experiencia en el procedimiento (119).

Para prevenir los eventos cerebrovasculares, se recomienda disminuir al mínimo las manipulaciones tanto en la raíz como en el anillo aórtico. Así, tanto las predilataciones como las postdilataciones deberían reservarse a los casos en los que fuesen absolutamente necesarias. Además, varios dispositivos de protección embólica tienen la aprobación de la Unión Europea, sin embargo, hasta el momento, su uso no se ha sistematizado y actualmente está aún limitado a los ensayos clínicos.

4.7. ALTERACIONES DE LA CONDUCCIÓN Y NECESIDAD DE IMPLANTE DE MARCAPASOS

La ocurrencia de trastornos de la conducción post-TAVR se ha atribuido a la proximidad de la válvula aórtica al sistema de conducción (nodo atrioventricular y fascículo izquierdo del Haz de Hiss). Así, tanto la existencia de un bloqueo de rama derecha previo (120), como los factores que incrementan la comprensión mecánica a este nivel se han asociado con una mayor incidencia de implante de marcapasos postprocedimiento: un implante más profundo de la prótesis, uso de prótesis autoexpandibles, uso de prótesis de mayor tamaño (29 y 31mm) y necesidad de

implante de una segunda válvula (121). Aunque esta complicación es menos frecuente en el acceso transapical que en el transfemoral (108), este hecho puede atribuirse a que la proporción de prótesis autoexpandibles (Vs balón-expandibles) es superior en la vía transfemoral. A este respecto, a pesar de que la necesidad de implante de marcapasos ha disminuido con la nueva generación de prótesis autoexpandibles, esta sigue siendo superior respecto a las prótesis balón-expandibles (12,7% CoreValve Evolute R Vs. 4,7% Edwards Sapien 3(122))

Recientes metaanálisis muestran que la ocurrencia de bloqueo de rama izquierda post-TAVR se asoció con mayor incidencia de necesidad de implante de marcapasos y muerte cardiovascular en el año siguiente al procedimiento (123). Por otra parte, aunque la necesidad de marcapasos en los 30 días post-TAVR no se asoció con mayor mortalidad al año, si parece estar relacionada con un deterioro en la FEVI, cuyo efecto a largo plazo aún no han sido bien esclarecido (121,124).

4.8. INSUFICIENCIA AÓRTICA RESIDUAL

La IAo post-TAVR constituye un importante factor pronóstico (125) y puede ser dividida en IAo transvalvular e IAo paravalvular. La IAo transvalvular o central es rara y puede estar causada por infraexpansión de la válvula o por disfunción de uno de los velos ocurrida durante el climpaje, la implantación o la postdilatación de la válvula. La IAo paravalvular es el tipo de IAo más frecuente tras TAVR y su ocurrencia se ha asociado con múltiples factores entre los cuales destacan: la presencia de calcificación importante a nivel de los velos o comisuras nativos, la inadecuada selección del tamaño de la prótesis o un posicionamiento incorrecto de la misma (126-131). Por todo ello, como se ha comentado previamente, el uso de técnicas de imagen tridimensionales para determinar las dimensiones y características del anillo es esencial para obtener adecuados resultados en un procedimiento de TAVR (80,132,133).

A pesar de que la incidencia de IAo moderada o severa tras TAVR continua siendo superior en comparación con la cirugía, los nuevos dispositivos han disminuido notablemente su incidencia(64,65). Así, se ha documentado un 3,7% de IAo moderada o severa con las válvulas Edwards Sapien XT y Sapien 3 en el estudio Partner 2 (64) y un 5,3% con las válvulas CoreValve y Core ValveEvolut R en el estudio SURTAVI(65). Se espera que cuando los estudios aleatorizados se realicen con dispositivos de tercera generación estas cifras sean aún menores, puesto que en estudios observacionales tanto la válvula Sapien 3 como la válvula Evolute R han mostrado incidencias de IAo moderada o severa menores del 1%(122).

Dado que, en ocasiones, la IAo paravalvular post-TAVR se compone de varios jets excéntricos, su cuantificación es compleja e hizo que en los primeros estudios, la incidencia de IAo publicada pudiera diferir mucho entre unos grupos y otros. Con el fin de unificar los criterios de valoración el documento de consenso VARC-2 estableció los parámetros para la evaluación de la IAo que se detallan en la **Tabla 4.** Respecto al diagnóstico, también se ha demostrado que la ecocardiografía tiende a infraestimar la severidad de la IAo en comparación con la resonancia magnética, por lo que ésa sería una técnica de utilidad en casos de duda diagnóstica (134).

	IAo Leve	IAo Moderada	IAo Severa
Parámetros Semicuantitativos			
Reversión del flujo diastólico en la aorta descendente	Ausente	Intermedio	Prominente Holodiastólico
Extensión circunferencial de la IAo	<10%	10-29%	≥30%
Parámetros Cuantitativos			
Volumen regurgitante (ml/latido)	<30ml	30-59ml	≥60 ml
% Fracción Regurgitante	<30%	30-49%	≥50%
EROA (cm^2)	<0,10 cm^2	0,10-0,29 cm^2	≥0,30 cm^2

Tabla 4: Parámetros Ecocardiográficos para la Valoración de la Severidad de la IAo post-TAVR (adaptado de Kappetein et Al (106))

4.9. DAÑO MIOCÁRDICO POSTPROCEDIMIENTO

La elevación de biomarcadores de necrosis miocárdica tras TAVR es frecuente, encontrándose algún grado de aumento de la CK-MB en hasta dos tercios de los pacientes si bien, el porcentaje de pacientes que cumple criterios VARC-2 para el diagnóstico de IM periprocedimiento (incremento >5 veces en los niveles de CK-MB por encima del límite de referencia de la normalidad) estaría en torno al 10% (135). El acceso transapical ($p<0,001$), la necesidad de implante de una segunda válvula ($p=0,016$) y las complicaciones mayores que impliquen conversión del procedimiento a cirugía abierta ($p<0,001$), se asociaron con mayor incidencia de IM periprocedimiento. El incremento en los niveles de CK-MB post-TAVR mostró un impacto negativo débil, pero significativo, en los cambios en la FEVI durante el seguimiento ($r= -0,17$; $p<0,001$). De igual forma, el incremento en los niveles de CK-MB se asoció con mayor mortalidad a los 30 días (OR para cada vez por encima del límite: 1,71; IC 95%: 1,25-2,35; $p<0,001$) y al año (HR para cada vez por encima del límite:1,32; IC 95%: 1,12-1,54; $p<0,001$).

5. PERSPECTIVAS Y RETOS FUTUROS

Anteriormente se ha comentado cómo la mejora en la selección de pacientes, en las técnicas de imagen y en los dispositivos utilizados han permitido reducir muchas de las complicaciones y extender la indicación a pacientes más jóvenes y de menor riesgo quirúrgico. Pese a ello, son muchas las cuestiones que aún quedan sin resolver en el campo del implante transcatéter de válvula aórtica.

Entre ellas cabe destacar:

- Los resultados hemodinámicos de los nuevos dispositivos valvulares de implante transcatéter que acceden al mercado.
- La durabilidad de las prótesis y la evolución de la hemodinámica valvular a medio y largo plazo, aspecto clave a la hora de tratar con esta técnica a pacientes más jóvenes y con mayor esperanza de vida.
- Cuál es el alcance y la repercusión clínica de la trombosis valvular subclínica post-TAVR y, en consecuencia, cuál debe ser el tratamiento antitrombotico/antiagregante más adecuado tras un procedimiento de TAVR.
- Cuáles deben ser los aspectos diferenciales a tener en cuenta en pacientes sometidos a TAVR tras un procedimiento de SAVR previo (procedimientos ViV)
- Determinar los factores predisponentes a una peor evolución y, por tanto a una mayor incidencia de rehospitalizaciones post-TAVR.
- El implante de prótesis transcatéter en pacientes con IAo pura.

El objetivo de la presente tesis es aportar información con respecto a varios de estos aspectos aún por dilucidar en el campo del TAVR, en especial en aquellos relacionados con la evolución clínica y hemodinámica tras un procedimiento de TAVR.

HIPÓTESIS

Las hipótesis de las que parten los estudios que dan lugar a los artículos que conforman la siguiente tesis doctoral serían las siguientes:

- El tratamiento de pacientes con EA grave y anillo aórtico pequeño mediante el implante de la válvula autoexpandible Portico daría lugar a resultados hemodinámicos a corto plazo equiparables a los obtenidos mediante el implante de la válvula balón-expandible Sapien XT.
- El aumento de gradiente medio tras un procedimiento de TAVR no es un hecho uniforme sino que afectaría predominantemente a una serie de pacientes en los que sería marcador de deterioro de la hemodinámica valvular. Factores trombóticos y de alteración de la dinámica de flujo valvular podrían estar asociados con una mayor incidencia de este deterioro.
- El implante de prótesis transcatéter en pacientes con bioprótesis aórticas tiene una serie de características diferenciales respecto a la preparación del procedimiento y a los resultados clínicos y hemodinámicos del mismo.
- Las rehospitalizaciones tempranas (<30 días post-TAVR) tendrían una repercusión negativa sobre el pronóstico clínico a medio plazo, por lo que es preciso identificar los factores asociados a una mayor incidencia de las mismas.

OBJETIVOS

Los objetivos de los estudios que conforman la presente tesis doctoral son los siguientes:

- Comparar los resultados hemodinámicos de la válvula autoexpandible Portico de 23 mm con los de la válvula balón-expandible Sapien XT de 23 mm mediante un estudio de casos apareados con análisis en un laboratorio central de ecocardiografía.
- Determinar la incidencia, cronología y predictores del deterioro de la hemodinámica valvular (definido como un aumento ≥10 mm Hg en el gradiente medio durante el seguimiento respecto al gradiente medio al alta) en una amplia cohorte de pacientes.
- Revisar la literatura disponible acerca de las características diferenciales de los procedimientos de TAVR en pacientes con bioprótesis quirúrgica previa (valve in valve).
- Identificar la incidencia, causas y predictores de reingresos hospitalarios tras un procedimiento de TAVR.

MATERIAL, MÉTODOS Y RESULTADOS

Artículo I: "Self-expanding Portico Valve Versus Balloon-expandable SAPIEN XT Valve in Patients With Small Aortic Annuli: Comparison of Hemodynamic Performance."*

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Original article

Self-expanding Portico Valve Versus Balloon-expandable SAPIEN XT Valve in Patients With Small Aortic Annuli: Comparison of Hemodynamic Performance

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ABSTRACT

Introduction and objectives: The self-expanding Portico valve is a new transcatheter aortic valve system yielding promising preliminary results, yet there are no comparative data against earlier generation transcatheter aortic valve systems. The aim of this study was to compare the hemodynamic performance of the Portico and balloon-expandable SAPIEN XT valves in a case-matched study with echocardiographic core laboratory analysis.

Methods: Twenty-two patients underwent transcatheter aortic valve implantation with the Portico 23-mm valve and were matched for aortic annulus area and mean diameter measured by multidetector computed tomography, left ventricular ejection fraction, body surface area, and body mass index with 40 patients treated with the 23-mm SAPIEN XT. Mean aortic annulus diameters were 19.6 ± 1.3 mm by transthoracic echocardiography and 21.4 ± 1.2 mm by computed tomography, with no significant between-group differences. Doppler echocardiographic images were collected at baseline and at 1-month of follow-up and were analyzed in a central echocardiography core laboratory.

Results: There were no significant between-group differences in residual mean transaortic gradients (SAPIEN XT: 10.4 ± 3.7 mmHg; Portico: 9.8 ± 1.1 mmHg; $P = .49$) and effective orifice areas (SAPIEN XT: 1.36 ± 0.27 cm^2; Portico, 1.37 ± .29 cm^2; $P = .54$). Rates of severe prosthesis-patient mismatch (effective orifice area < 0.65 cm^2/m^2) were similar (SAPIEN XT: 13.5%; Portico: 10.0%; $P = .56$). No between-group differences were found in the occurrence of moderate-severe paravalvular leaks (5.0% vs 4.8% of SAPIEN XT and Portico respectively; $P = .90$).

Conclusions: Transcatheter aortic valve implantation with the self-expanding Portico system yielded similar short-term hemodynamic performance compared with the balloon-expandable SAPIEN XT system for treating patients with severe aortic stenosis and small annuli. Further prospective studies with longer-term follow-up and in patients with larger aortic annuli are required.

Válvulas Portico y SAPIEN XT en el tratamiento de pacientes con anillo aórtico pequeño: comparación de resultados hemodinámicos

Palabras clave:
Estenosis aórtica
Implante percutáneo de válvula aórtica
Desajuste prótesis-paciente
Insuficiencia aórtica

RESUMEN

Introducción y objetivos: La válvula autoexpandible Portico es una nueva válvula de implante transcatéter que ha mostrado resultados prometedores en estudios preliminares; sin embargo, no existen estudios que comparen este dispositivo con sistemas previos de válvula aórtica transcatéter. El objetivo de este estudio es comparar los resultados hemodinámicos de la válvula autoexpandible Portico con los de la válvula expandible por balón SAPIEN XT en un estudio de casos apareados con análisis en un laboratorio central de ecocardiografía

Métodos: Se emparejó a 22 pacientes tratados mediante implante transcatéter de la válvula Portico de 23 mm con 40 pacientes tratados con la válvula SAPIEN XT de 23 mm, según los siguientes parámetros: área y diámetro medio del anillo aórtico por tomografía computarizada multidetector, fracción de eyección del ventrículo izquierdo, área de superficie corporal e índice de masa corporal. El diámetro medio del anillo aórtico fue de 19,6 ± 1,3 mm por ecocardiografía transtorácica y de 21,4 ± 1,2 mm por

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tomografía computarizada, sin diferencias significativas entre los grupos. Se obtuvieron imágenes de ecocardiografía Doppler antes de la intervención y en el seguimiento realizado al cabo de 1 mes y se analizaron en un laboratorio central de ecocardiografía.

Resultados: No se objetivaron diferencias significativas entre los grupos en el gradiente transaórtico medio residual (SAPIEN XT, 10,4 ± 3,7 mmHg; Portico, 9,8 ± 1,1 mmHg; p = 0,49) ni en el área efectiva del orificio valvular (SAPIEN XT, 1,36 ± 0,27 cm^2; Portico, 1,37 ± 0,29 cm^2; p = 0,54). La incidencia del desajuste protésico (área efectiva del orificio valvular < 0,65 cm^2/m^2) fue similar en ambos grupos (el 13,5 frente al 10,0%; p = 0,56). No se observaron diferencias entre los grupos en cuanto a la incidencia de fugas paravalvulares moderadas o graves (el 5,0 frente al 4,8%; p = 0,90).

Conclusiones: El implante transcatéter de la válvula autoexpandible Portico produjo resultados hemodinámicos a corto plazo similares a los de la válvula expandible por balón SAPIEN XT en el tratamiento de pacientes con estenosis aórtica grave y anillo aórtico pequeño. Son necesarios estudios prospectivos con seguimiento a más largo plazo y en pacientes con anillo aórtico mayor.

Abbreviations

EOA: effective orifice area
MDCT: multidetector computed tomography
PPM: prosthesis-patient mismatch
SXTV: SAPIEN XT valve
TAVI: transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is well-established for treating patients with symptomatic severe aortic stenosis deemed at high or prohibitive risk for surgical aortic valve replacement.[1] Moreover, TAVI has been associated with improved hemodynamic and clinical outcomes in patients with small aortic annuli, with a lower incidence of prosthesis-patient mismatch (PPM) and a nonsignificant increase in significant aortic regurgitation (AR) compared with surgical aortic valve replacement in this group of patients.[2–4] However, data on the treatment of patients with small annuli has been mainly limited to the use of small (23 mm) balloon-expandable transcatheter valves.

The Portico valve system (St. Jude Medical; Minneapolis, Minnesota, United States) is a second-generation transcatheter aortic valve consisting of a nitinol self-expanding frame containing 3 bovine pericardial leaflets and a porcine pericardial sealing cuff[5] (Figure 1). The ability to retrieve and reposition the Portico valve represents 2 important positive features of this new valve system. The first available Portico valve was 23-mm size, and preliminary data in a small patient cohort demonstrated satisfactory clinical and hemodymamic outcomes in patients with small aortic annuli.[6] However, it is well known that the lower amount of metal in the Portico stent frame, facilitating the ability to completely resheath a positioned valve, results in the production of lower radial forces compared with other self-expanding transcatheter aortic valve systems.[7] This has raised concerns about how such changes may impact transcatheter valve performance (paravalvular leak rate and residual valve areas). In addition, the lower insertion of the valve leaflets within the stent frame, at the annular instead of supra-annular level, may also negatively impact valve hemodynamics. It would therefore be important to compare the hemodynamic performance of this valve with that of prior generation valves. Our objective was to compare the short-term hemodynamic performance of the 23-mm self-expanding Portico valve with the 23-mm balloon-expandable SAPIEN XT valve (SXTV) as evaluated in a case-matched population by a central echocardiography laboratory in patients with small aortic annuli.

METHODS

Across 2 centers, 22 consecutive patients with severe symptomatic aortic stenosis underwent TAVI with the 23-mm self-expanding Portico valve. These patients were matched against 40 consecutive patients who had previously undergone TAVI with the 23-mm balloon expandable SXTV. Data from these patients had been prospectively acquired. The matching criteria (all pre-TAVI) involved: *a)* prosthesis size (23 mm, exact match); *b)* aortic annulus area (within 50 mm^2) as assessed by multidetector computed tomography (MDCT); *c)* mean aortic annulus diameter as assessed by MDCT (within 0.5 mm); *d)* left ventricular ejection fraction (within 10%) measured by transthoracic echocardiography; *e)* body surface area (within 0.4 m^2), and *f)* body mass index (within 5 kg/m^2). A variable number of controls (from 1 to 4) were used, leading to a final sample of 40 matched patients who had undergone TAVI with the 23-mm SXTV. The values of the matched variables, according to valve type, are listed in Table 1.

Multidetector computed tomography examinations were performed and interpreted according to the criteria recommended by Achenbach et al.[8] Briefly, the MDCT acquisition protocol was electrocardiogram gated (in systole), during suspended respiration, with a system of 64 simultaneously acquired slices and administration of iodinated contrast medium. Reconstruction of 0.6 mm slice width throughout the entire imaging volume was obtained.

Prosthesis sizing was determined on the basis of aortic annulus measurements as previously described.[5,9] The objective was to obtain a 1% to 15% prosthesis area oversizing with respect to the aortic annulus area in all patients. The TAVI procedure has been explained in detail in prior publications.[1] The procedures were guided by fluoroscopy/angiography and transesophageal echocardiography. Procedural data and 30-day clinical events were prospectively recorded and defined according to the Valve Academic Research Consortium-2 (VARC-2) criteria.[10] All TAVI procedures were performed under a compassionate clinical use program approved by Health Canada, and all patients provided signed informed consent.

All patients underwent a complete transthoracic echocardiographic examination, according to the guidelines of the American Society of Echocardiography,[11,12] before the procedure and within 30 days post-TAVI. All echocardiographic examinations were centrally evaluated in the echocardiography core laboratory of the Quebec Heart and Lung Institute. All images were stored in digital format, and the analyses were performed off-line by experienced technicians and supervised by a cardiologist using an Image Arena Platform (TomTec Imaging Systems; Unterschleissheim, Germany). The following measurements were obtained for all patients: aortic annulus diameter, left ventricular outflow tract tract (LVOT) diameter, stroke volume, left ventricular ejection

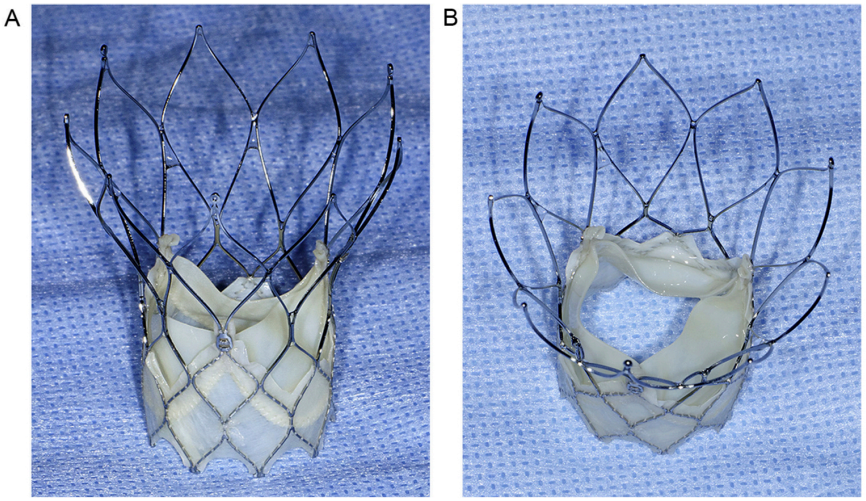

Figure 1. A and B) St. Jude Medical Portico transcatheter heart valve consisting of 3 bovine pericardial leaflets attached on a nitinol stent.

Table 1
Matched Variables (Each Group Received the 23-mm Prosthesis)

Variable	Valve type			OR (95%CI)	*P*
	All (n = 62)	SAPIEN XT (n = 40)	Portico (n = 22)		
Mean aortic annulus diameter, mm	21.4 ± 1.2	21.7 ± 1.1	20.9 ± 1.2	0.57 (0.19-1.74)	.324
Aortic annulus area, mm^2	369.9 ± 36.6	373.6 ± 33.0	364.3 ± 42.3	1.00 (0.97-1.04)	.934
LVEF, %	56.9 ± 11.9	58.1 ± 10.9	54.8 ± 13.7	0.95 (0.88-1.03)	.189
Body surface area, m^2	1.58 ± 0.13	1.57 ± 0.12	1.60 ± 0.14	3.18 (0.05-213.20)	.589
BMI	23.5 ± 3.9	23.9 ± 4.2	22.8 ± 3.5	0.90 (0.77-1.06)	.197

95%CI, 95% confidence interval; BMI, body mass index; LVEF, left ventricular ejection fraction; OR, odds ratio.
Assessed by computed tomography.
Unless otherwise indicated, data are expressed as mean ± standard deviation.

fraction evaluated using the biplane Simpson method, the mean and peak transvalvular gradient estimated with the modified Bernoulli formula, and valve effective orifice area (EOA) calculated using the continuity equation. The aortic annulus was measured in a zoomed parasternal long-axis view from the hinge point of the anterior aortic cusp and the ventricular septum to the junction of the posterior aortic cusp and the anterior mitral leaflet. After TAVI, LVOT diameter was measured just beneath the apical margin of the prosthesis stent.[10,13,14] The LVOT Doppler recordings were also obtained just below the stent margin to ensure that the flow velocities were recorded at the same location as the LVOT.[14,15] If the transcatheter valve was positioned low in the LVOT, with the stent margin below the apical end of the LVOT and protruding in the left ventricular cavity, the measurements of the LVOT diameter and velocity were obtained within the stent just below the transcatheter valve leaflets.[16] The Doppler velocity index was calculated as the LVOT velocity/transvalvular velocity ratio.[15,17] The EOA was indexed to the body surface area, and the presence of PPM was defined as an indexed EOA $\leq 0.85\ cm^2/m^2$. A PPM was considered to be moderate if the indexed EOA was $0.65\ cm^2/m^2$ to $0.85\ cm^2/m^2$, and severe if the indexed EOA was $< 0.65\ cm^2/m^2$.[18]

The presence, degree, and type (paravalvular or transvalvular) of AR were recorded in all patients. The AR severity was evaluated using a multiparametric approach and classified following the VARC-2 recommendations. The severity of AR was classified as follows: none-trace, mild, moderate, and severe. In the presence of paravalvular AR, the number of jets, localization, and the circumferential extent were also assessed. The circumferential extent of the paravalvular jets was measured in the parasternal short-axis views with color Doppler.[14,15]

Statistic Analysis

Each matched group was considered as a stratification variable. Conditional logistic regression was performed to detect association between valve type and selected variables observed in strata. The results were considered significant with P values < 0.05.

Analyses were conducted using the statistical packages SAS, version 9.3 (SAS Institute Inc.; Cary, North Carolina, United States).

RESULTS

There were no significant between-group differences in baseline clinical characteristics, but there was a trend towards a higher prevalence of women in the SXTV group (Table 2). The main procedural and in-hospital events post-TAVI are listed in Table 3. There were no significant between-group differences in periprocedural events, although there was a nonsignificantly greater incidence of major bleeding in the Portico group compared with the SXTV group (14.3% vs 5.0%; $P = .081$). The rate of pacemaker implantation was low (< 10%) in the 2 groups. Two patients in the Portico group required second valve implantation. In 1 patient, severe AR was observed after first valve deployment. In another patient, the Portico valve embolized into the ascending aorta

Table 2
Baseline Characteristics, Overall and According to Transcatheter Valve Type

Variable	Valve type			OR (95%CI)	*P*
	All (n = 62)	SAPIEN XT (n = 40)	Portico (n = 22)		
Age, y	81.5 ± 6.2	81.2 ± 6.5	82.0 ± 5.9	1.05 (0.95-1.16)	.370
Female sex	48 (77.4)	39 (97.5)	9 (40.9)	0.149 (0.0-0.821)	.063
Body surface area, m^2	1.58 ± 0.13	1.57 ± 0.12	1.60 ± 0.14	3.18 (0.05-213.90)	.589
NYHA functional class III-IV	41 (68.3)	26 (66.7)	15 (71.4)	1.08 (0.33-3.51)	.899
BMI	23.5 ± 3.9	23.9 ± 4.2	22.8 ± 3.5	0.90 (0.77-1.06)	.197
Hypertension	50 (80.7)	35 (87.5)	15 (68.2)	0.34 (0.09-1.23)	.099
Dyslipidemia	44 (70.9)	29 (72.5)	15 (68.2)	0.84 (0.26-2.73)	.767
Diabetes mellitus	17 (27.4)	9 (22.5)	8 (36.4)	1.91 (0.52-6.99)	.326
Chronic atrial fibrillation	7 (14.3)	5 (12.5)	2 (22.2)	3.21 (0.41-25.20)	.269
Coronary artery disease	30 (48.4)	22 (55.0)	8 (36.4)	0.46 (0.15-1.37)	.163
Prior CABG	13 (26.5)	12 (30.0)	1 (11.1)	3.00 (0.00-57.00)	1.00
Cerebrovascular disease	8 (16.3)	8 (20.0)	0 (0.0)	1.00 (0.00-8.47)	1.00
COPD	13 (20.9)	10 (25.0)	3 (13.6)	0.33 (0.07-1.62)	.172
eGFR mL/min/$1.73m^2$	64.2 ± 21.5	67.8 ± 23.2	57.8 ± 16.8	0.98 (0.96-1.01)	.129
STS-PROM, %	6.8 ± 2.8	6.6 ± 2.6	7.1 ± 3.2	1.00 (0.83-1.22)	.967

95%CI, 95% confidence interval; BMI, body mass index; CABG, coronary arterial bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; OR, odds ratio; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality.
Unless otherwise indicated, data are expressed as No. (%) or mean ± standard deviation.

during the snaring maneuvers for valve repositioning, a second valve was successfully implanted. In a third patient, the valve moved toward the LVOT at the end of the deployment and it was implanted slightly more ventricularly than expected; however, no significant AR or hemodynamic repercussions were observed. In the same way, 2 patients treated with the SXTV required a second valve because of severe AR after first valve deployment that persisted following balloon post-dilatation. One patient in the SXTV group had a ventricular perforation (wire-related) requiring conversion to open surgery.

The main echocardiography and MDCT characteristics according to valve type are listed in Table 4. There were no between-group differences in the severity of aortic stenosis ($P > .70$ for mean transvalvular gradient and aortic valve area), and aortic annulus diameter (as evaluated by transthoracic echocardiography) was also similar between the 2 groups ($P = .30$). Apart from the matched MDCT variables (aortic annulus area and mean diameter), the 2 groups were also well balanced with regards to the aortic annulus eccentricity index ($P = .21$). Also, the degree of valve oversizing was similar in the Portico and SXTV groups (10.4 ± 6.6% vs 6.5 ± 5.6%; $P = .31$).

Echocardiographic data post-TAVI, according to valve type, are listed in Table 5. Left ventricular outflow tract measurements of diameter and velocity were performed prestent in all patients, according the recommendations of VARC-2. The overall mean transprosthetic gradient decreased from 45.2 ± 16.1 mmHg to 10.2 ± 4.1 mmHg ($P < .001$), and the mean EOA increased from 0.60 ± 0.2 cm^2 to 1.36 ± 0.28 cm^2 ($P < .001$) post-TAVI. There were no between-group differences in residual transaortic mean gradients ($P = .49$) and EOAs ($P = .54$). No between-group differences were found in the presence and severity of paravalvular leaks ($P = .90$) or total AR ($P = .95$) (Figures 2 and 3).

DISCUSSION

This first report comparing the hemodynamic performance of the newer 23-mm self-expanding Portico valve with the 23-mm

Table 3
Post-procedural Complications According to Transcatheter Valve Type

Variable	Valve type			OR (95%CI)	*P*
	All (n = 62)	SAPIEN XT (n = 40)	Portico (n = 22)		
Approach					
Transfemoral	36 (58.1)	21 (52.5)	15 (68.2)	1.92 (0.62-5.90)	.259
Transapical/transaortic	26 (41.9)	19 (47.5)	7 (31.8)		
Conversion to open heart surgery	1 (2.2)	1 (3.7)	0 (0.0)	1.00 (0.00-19.00)	1.00
Need for a second valve	4 (6.5)	2 (5.0)	2 (9.1)	3.51 (0.31-40.20)	.312
Balloon post-dilation	13 (20.9)	11 (27.5)	2 (9.1)	0.43 (0.08-2.18)	.311
Valve embolization	1 (2.2)	0 (0.0)	1 (4.5)	5.30 (0.20-31.20)	.291
Pacemaker	4 (6.6)	3 (7.5)	1 (4.5)	0.52 (0.05-5.25)	.576
Stroke	4 (6.5)	2 (5.0)	2 (9.1)	1.82 (0.23-14.60)	.573
Myocardial infarction	2 (3.3)	2 (5.0)	0 (0.0)	1.29 (0.00-11.60)	1.00
Major bleeding	5 (8.2)	2 (5.0)	3 (14.3)	5.21 (0.82-33.10)	.081

95%CI, 95% confidence interval; OR, odds ratio.
Unless otherwise indicated, data are expressed as No. (%).

Table 4
Echocardiography and Computed Tomography Data at Baseline, Overall and According to Valve Type

Variable	Valve type			OR (95%CI)	*P*
	All (n = 62)	SAPIEN XT (n = 40)	Portico (n = 22)		
Echocardiographic variables					
Aortic annulus mean diameter TTE, mm	19.6 ± 1.3	19.7 ± 1.4	19.4 ± 1.2	0.73 (0.41-1.32)	.299
LVEF (%)	56.9 ± 11.9	58.1 ± 10.9	54.8 ± 13.7	0.95 (0.88-1.03)	.189
Peak aortic gradient, mmHg	73.8 ± 25.2	77.9 ± 24.3	69.8 ± 25.9	0.99 (0.96-1.02)	.549
Mean aortic gradient, mmHg	45.2 ± 16.1	47.4 ± 15.5	42.8 ± 13.0	0.99 (0.95-1.04)	.714
AVA, cm^2	0.60 ± 0.20	0.58 ± 0.23	0.62 ± 0.16	0.49 (0.01-32.50)	.736
PASP, mmHg	40.7 ± 12.2	37.8 ± 10.8	45.8 ± 13.0	1.10 (1.02-1.18)	.019
Aortic regurgitation grade					
None/trace	17 (27.9)	11 (27.5)	6 (28.6)	1.04 (0.40-2.76)	.691
Mild	38 (62.3)	25 (62.5)	13 (61.9)		
Moderate/severe	6 (9.8)	4 (10.0)	2 (9.5)		
Mitral regurgitation grade					
None/trace	2 (3.3)	1 (2.5)	1 (5.0)	1.92 (0.64-5.81)	.247
Mild	32 (53.3)	23 (57.5)	9 (45.0)		
Moderate/severe	26 (43.3)	16 (40.0)	10 (50.0)		
Computed tomography					
Aortic annulus mean diameter, mm	21.4 ± 1.20	21.7 ± 1.12	20.9 ± 1.22	0.57 (0.19-1.74)	.324
Eccentricity index	0.80 ± 0.07	0.81 ± 0.06	0.78 ± 0.09	0.001 (0.00-38.60)	.207
Aortic annulus area, mm^2	369.9 ± 36.6	373.6 ± 33.0	364.3 ± 42.3	1.00 (0.97-1.04)	.934
Prosthesis oversizing, %	7.9 ± 6.2	6.5 ± 5.6	10.4 ± 6.6	1.12 (0.91-1.38)	.306

95%CI, 95% confidence interval; AVA, aortic valve area; LVEF, left ventricular ejection fraction; OR, odds ratio; PASP, pulmonary artery systolic pressure; TTE, transthoracic echocardiography.
Unless otherwise indicated, data are expressed as No. (%) or mean ± standard deviation.

Table 5
Echocardiography Data Post-transcatheter Aortic Valve Implantation According to Valve Type

Variable	Valve type			OR (95%CI)	*P*
	All (n = 62)	SAPIEN XT (n = 40)	Portico (n = 22)		
LVEF, %	60.6 ± 13.6	61.9 ± 11.5	58.3 ± 16.6	0.98 (0.93-1.03)	.354
Peak aortic gradient, mmHg	19.3 ± 7.3	19.7 ± 6.5	18.6 ± 8.9	0.96 (0.88-1.05)	.372
Mean aortic gradient, mmHg	10.2 ± 4.1	10.4 ± 3.7	9.8 ± 1.1	0.95 (0.83-1.09)	.488
AVA, cm^2	1.36 ± 0.28	1.36 ± 0.27	1.37 ± 0.29	1.92 (0.25-15.00)	.535
Total Aortic regurgitation grade					
None/trace	25 (41.0)	17 (42.5)	8 (38.1)	1.41 (0.46-4.30)	.953
Mild	33 (54.1)	21 (52.5)	12 (57.1)		
Moderate/severe	3 (4.9)	2 (5.0)	1 (4.8)		
Paravalvular aortic regurgitation grade					
None/trace	26 (42.6)	18 (45.0)	8 (38.1)	1.48 (0.49-4.51)	.901
Mild	32 (52.5)	20 (50.0)	12 (57.1)		
Moderate/severe	3 (4.9)	2 (5.0)	1 (4.8)		
Central aortic regurgitation grade					
None/trace	57 (93.4)	37 (92.5)	20 (95.2)	0.55 (0.04-7.14)	1.00
Mild	4 (6.6)	3 (7.5)	1 (4.8)		
Moderate/severe	0 (0)	0 (0)	0 (0)		
Mitral regurgitation grade					
None/trace	3 (5.4)	2 (5.4)	1 (5.3)	1.44 (0.50-4.10)	.717
Mild	34 (60.7)	24 (64.9)	10 (52.6)		
Moderate/severe	19 (33.9)	11 (29.7)	8 (42.1)		
PPM					
None	35 (61.4)	23 (62.2)	12 (60.0)	0.83 (0.36-1.91)	.662
Moderate	15 (26.3)	9 (24.3)	6 (30.0)		
Severe	7 (12.3)	5 (13.5)	2 (10.0)		
Moderate/severe PPM	22 (38.6)	14 (37.8)	8 (40.0)	0.87 (0.27-2.78)	.812
Severe PPM	7 (12.3)	5 (13.5)	2 (10.0)	0.58 (0.09-3.71)	.561

95%CI, 95% confidence interval; AVA, aortic valve area; LVEF, left ventricular ejection fraction; OR, odds ratio; PPM, patient prosthesis mismatch.
Unless otherwise indicated, data are expressed as No. (%) or mean ± standard deviation.

balloon-expandable SXTV for treating patients with severe aortic stenosis and small aortic annuli highlights similar hemodynamic performances for the 2 valve systems, with mean residual gradients < 10 mmHg and rates of severe PPM < 15%. In addition, the rate of moderate or severe paravalvular leaks was ~5% in the groups.

Some, but not all, previous studies demonstrated higher earlier paravalvular leak rates with the use of the self-expanding CoreValve system.[19–22] Although long-term differences between valves are uncertain, this higher earlier paravalvular leak incidence was partially attributed to a lower achieved radial force as compared with the balloon-expandable Edwards system.[23] Subsequent concerns were therefore raised about the newer Portico self-expanding transcatheter aortic valve system, largely due to its reduced amount of metal and cell size of the stent frame also resulting in a lower radial force akin to the CoreValve system.[7] These design features were incorporated with the objective of producing a fully retrievable and repositionable transcatheter aortic valve system in the advent of valve malpositioning or embolization. The present report confirms that these design features did not translate into a greater occurrence and heightened severity of paravalvular leaks. The larger cell area design results in a high tissue to frame ratio at the valve cuff segment, which has been proposed as a potential mechanism of reducing AR by allowing valve tissue to conform around calcific nodules at the annular level. Furthermore, it is now well accepted that proper device positioning is a key factor related to the occurrence of AR.[24] In this regard, the repositionable-retrievable nature of the Portico transcatheter aortic system may contribute to an improved final positioning of the valve.

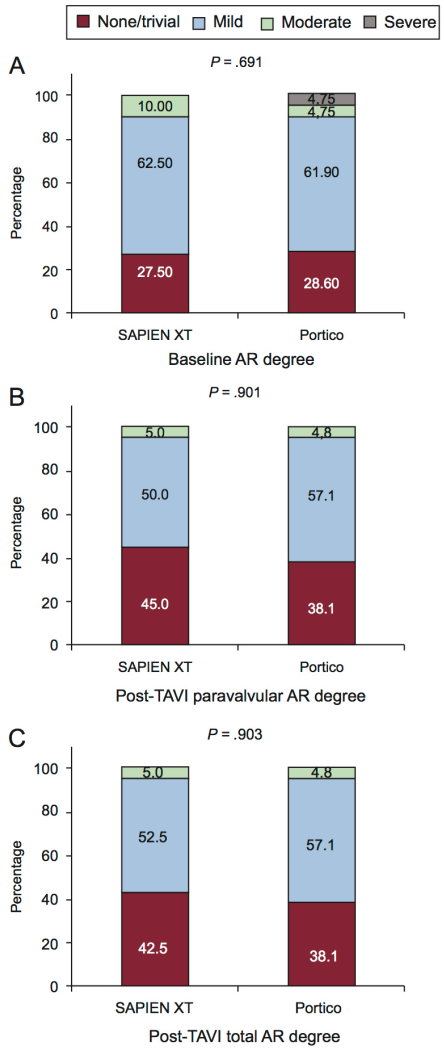

Figure 2. Baseline (A), paravalvular (B), and global (C) aortic regurgitation after transcatheter aortic valve implantation, according to the valve type (SAPIEN XT or Portico valve). AR, aortic regurgitation; TAVI, transcatheter aortic valve implantation.

The occurrence of PPM post-TAVI (and surgical aortic valve replacement) remains a major concern following the treatment of patients with severe aortic stenosis and small annuli. Two recent substudies of the PARTNER trial,[2,3] demonstrated lower PPM rates post-balloon-expandable TAVI compared with surgical aortic valve replacement in such patients. In addition to the lower radial force imparted by the Portico valve, the fact that the valve leaflets are positioned very low (at the annular instead of supra-annular level) within the stent frame could have translated into increased residual gradients and higher PPM rates. The present study outlined a mean residual gradient of < 10 mmHg and a 40% moderate or severe PPM rate following Portico valve implantation in patients with small annuli, similar to the results obtained with the balloon-expandable Edwards system. This rate is also in accordance with the PPM rate reported in prior studies in patients with small annuli.[3,4] The adaptability and normal valve functioning of the Portico system has been proven in circular and noncircular structures in bench testing (unpublished data) and this likely assists in maintaining the low residual gradients despite the lower radial forces. Future studies are needed to evaluate how this system compares with other TAVI systems with supra-annular valvular function properties (ie, Medtronic CoreValve system).

St. Jude Medical temporarily halted the Portico valve program in September 2014 following the detection of reduced valve leaflet mobility as evaluated by 4-dimensional MDCT among patients participating in the United States pivotal trial (ClinicalTrials.gov: 02000115). This decision was undertaken even though preliminary clinical and echocardiography data failed to suggest any issues with the valve system. The present study confirms that early valve hemodynamics of the Portico system are comparable to contemporary TAVI systems. Importantly, a lack of increased residual gradients and the absence of cases of significant transvalvular AR were observed. Unfortunately, no transesophageal echocardiography or contrast MDCT exams were performed at follow-up in our study population, and no additional data to current knowledge on valve leaflet motion can be provided.

Although this study was not powered to detect differences in clinical events, no significant differences were found in early events between groups. No cases of valve thrombosis were reported, which is consistent with the previously reported low incidence of this complication.[25] Of note, the permanent pacemaker implantation rate was low in both groups, particularly in the Portico group (4.8%). This incidence is much lower than contemporary data from other self-expanding transcatheter aortic valves,[26] and may be partially due to the specific design of the Portico valve system. Compared with the CoreValve system, the Portico valve does not contain a flared inflow and it presents leaflets and a tissue cuff located low on the support frame, thereby minimizing device protrusion into the LVOT. In addition, deep valve implantation has been reported as an independent factor predicting the need for permanent pacemaker implantation post-TAVI with self-expanding valves.[26] Due to the ability to completely resheath, the Portico valve can be repositioned in order to avoid lower implantation.

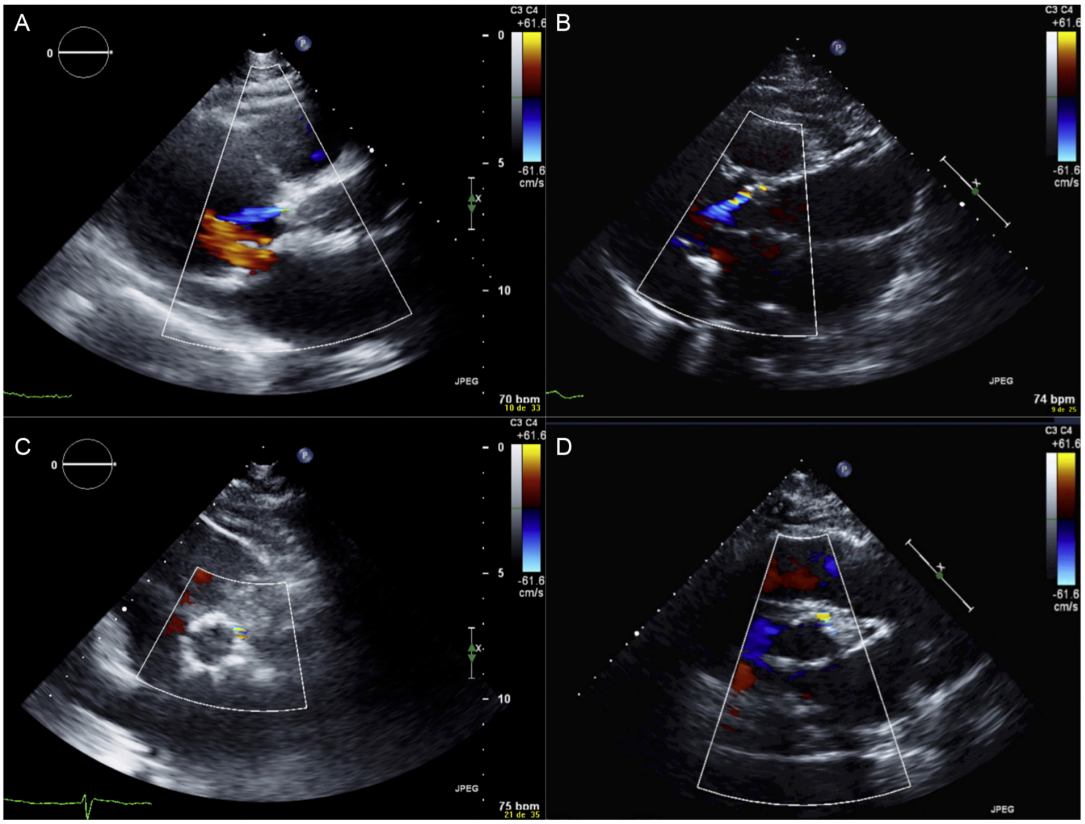

Figure 3. Postprocedural echocardiographic images of 2 patients who had undergone transcatheter aortic valve implantation with the Portico valve (A and C) and the SAPIEN XT valve (B and D). Mild paravalvular leak after Portico valve implantation (A: long axis; C: short axis) and SAPIEN XT valve implantation (B: long axis; D: short axis).

Limitations

Several caveats of the present analysis warrant further consideration, including its nonrandomized design and limited sample size. This was partially compensated by a strict matching process between groups, including 3-dimensional MDCT data, and a uniform standardized analysis performed by a central echocardiography core laboratory. However, these results need to be confirmed by a larger, prospectively designed randomized trial. As expected when evaluating a new transcatheter heart valve, both centers had less experience with the Portico valve compared with their experience of SXTV. Only patients who survived the hospitalization period were included in the present analysis, and, as a result, there may have been a possible "positive" patient selection bias in both groups. Also, no systematic data on calcium burden at the valve-annulus level (a factor that may influence the incidence of paravalvular leaks) were obtained in this study, precluding the use of this variable for the matching process. These data refer to tricuspid aortic valves, future studies in bicuspid aortic stenosis are needed.[27] Finally, these data apply exclusively to the 23-mm valve and cannot be extrapolated to larger aortic annuli and valve sizes.

CONCLUSIONS

The 23-mm self-expanding Portico valve system was associated with a similar hemodynamic performance to the balloon-expandable SXTV system. While we await the results of the prospective randomized United States pivotal trial, the present report suggest that the Portico valve system could be a valid alternative for treating patients with severe aortic stenosis and small aortic annuli.

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CONFLICTS OF INTEREST

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Artículo II: "Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement: Multicenter Registry."

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Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement

Multicenter Registry

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ABSTRACT

BACKGROUND Scarce data exist on the incidence of and factors associated with valve hemodynamic deterioration (VHD) after transcatheter aortic valve replacement (TAVR).

OBJECTIVES This study sought to determine the incidence, timing, and predictors of VHD in a large cohort of patients undergoing TAVR.

METHODS This multicenter registry included 1,521 patients (48% male; 80 ± 7 years of age) who underwent TAVR. Mean echocardiographic follow-up was 20 ± 13 months (minimum: 6 months). Echocardiographic examinations were performed at discharge, at 6 to 12 months, and yearly thereafter. Annualized changes in mean gradient (mm Hg/year) were calculated by dividing the difference between the mean gradient at last follow-up and the gradient at discharge by the time between examinations. VHD was defined as a ≥10 mm Hg increase in transprosthetic mean gradient during follow-up compared with discharge assessment.

RESULTS The overall mean annualized rate of transprosthetic gradient progression during follow-up was 0.30 ± 4.99 mm Hg/year. A total of 68 patients met criteria of VHD (incidence: 4.5% during follow-up). The absence of anticoagulation therapy at hospital discharge ($p = 0.002$), a valve-in-valve (TAVR in a surgical valve) procedure ($p = 0.032$), the use of a 23-mm valve ($p = 0.016$), and a greater body mass index ($p = 0.001$) were independent predictors of VHD.

CONCLUSIONS There was a mild but significant increase in transvalvular gradients over time after TAVR. The lack of anticoagulation therapy, a valve-in-valve procedure, a greater body mass index, and the use of a 23-mm transcatheter valve were associated with higher rates of VHD post-TAVR. Further prospective studies are required to determine whether a specific antithrombotic therapy post-TAVR may reduce the risk of VHD. (J Am Coll Cardiol 2016;67:644-55)

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Structural valve degeneration (SVD) is the main cause of bioprosthetic valve failure after surgical aortic valve replacement (SAVR). The reported incidence of SVD after SAVR at 1, 10, and 15 years has been <1%, 10% to 30%, and 20% to 50%, respectively (1–3). These data traditionally have been determined on the basis of the incidence of reoperation after surgical bioprosthetic valve failure. However, this approach may underestimate the true incidence of SVD (4,5), and several studies have proposed to define SVD occurrence according to the development of valve hemodynamic dysfunction documented by Doppler echocardiography (6–8). With this approach, Mahjoub et al. (8) found a 20% SVD incidence during a mean follow-up of 8 years post-SAVR. Valve hemodynamic deterioration (VHD) as documented by Doppler echocardiography may be related to calcific degeneration of bioprosthetic valve leaflets (i.e., SVD), but it may also result from thrombosis or pannus ingrowth.

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Transcatheter aortic valve replacement (TAVR) is well established for treating patients with symptomatic severe aortic stenosis who are at high or prohibitive surgical risk (9). Although SVD requiring valve replacement is a rare entity within the first years after TAVR (10,11), scarce data exist on subclinical bioprosthetic hemodynamic dysfunction after TAVR. Investigators have suggested that rapid changes in transvalvular gradients may be the hallmark of valve thrombosis despite the absence of clinical symptoms (12–14). Given that antithrombotic or anticoagulation therapies post-TAVR are not currently well established, it is of the utmost importance to determine whether subclinical valve thrombosis could be an underlying pathophysiological mechanism contributing to transcatheter valve failure. We aimed to establish the incidence and risk factors of VHD within a large population of patients who had undergone TAVR.

METHODS

Between May 2007 and October 2014, 2,418 consecutive patients underwent TAVR in 10 participating centers. Patients were considered eligible for this multicenter study if they had undergone at least 2 echocardiograms post-TAVR (at discharge and at a minimum of 6- to 12-month follow-up). A total of 1,521 patients satisfied these criteria and were included in our study. Eligibility for TAVR, valve type, and access route were determined at each center by a local heart team composed of interventional cardiologists and cardiac surgeons. Clinical, procedural, and echocardiographic data were prospectively gathered within a TAVR database at each participating center. This study was not a prespecified analysis at the time of the creation of the database; therefore, data were analyzed retrospectively. Clinical follow-up was undertaken during clinical visits or through telephone contact, or both, at 1 month post-TAVR, at 6 to 12 months post-TAVR, and yearly thereafter in all participating centers. Clinical events were prospectively recorded and defined according to VARC-2 (Valve Academic Research Consortium-2) criteria (15).

ECHOCARDIOGRAPHIC ASSESSMENT. Transthoracic echocardiography (TTE) examinations were performed at baseline, at hospital discharge, at 6 to 12 months post-TAVR, and yearly thereafter.

All TTE examinations were conducted according to American Society of Echocardiography guidelines (16,17). Peak transprosthetic flow velocity was determined by continuous-wave Doppler imaging. The mean transprosthetic gradient was calculated using the modified Bernoulli formula. Absolute change in mean gradient was calculated as the gradient at last follow-up minus the gradient at discharge. Annualized change in mean gradient (mm Hg/year) was calculated by dividing the absolute change in gradient by the time between examinations. VHD was defined as an absolute change in gradient of ≥10 mm Hg during follow-up (8,18). Early VHD was defined as a ≥10 mm Hg increase in mean gradient within the first year after TAVR compared with discharge assessment. Moderate and severe postoperative prosthesis-patient mismatches (PPMs) were defined as an indexed effective orifice area (EOA) of ≥0.65 to ≤0.85 cm^2/m^2 and <0.65 cm^2/m^2, respectively (19).

STATISTICAL ANALYSIS. Categorical variables are reported as number (percent) and continuous variables as mean ± SD or median (25th to 75th interquartile range [IQR]), depending on variable distribution. Group comparisons were analyzed with the Student *t* test or Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Changes in mean transaortic gradient measurements over time (discharge, 6 months to 1, 2, 3, and 4 years) were evaluated with repeated-measures analyses of variance. The normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the Cholesky factorization of the statistical model. Mean

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
BMI = body mass index
CT = computed tomography
EOA = effective orifice area
PPM = prosthesis-patient mismatch
SAVR = surgical aortic valve replacement
SVD = structural valve degeneration
TAVR = transcatheter aortic valve replacement
TE = transthoracic echocardiography
TEE = transesophageal echocardiography
THV = transcatheter heart valve
VHD = valve hemodynamic deterioration

gradient elevation values were log-transformed to stabilize variances. The predictors of mean gradient progression were determined using linear regression analyses. Univariable and multivariable Cox proportional hazards models were used to identify potential determinants of VHD over time. Univariable and multivariable logistic regression analyses were used to identify independent factors associated with VHD within the first year post-TAVR. The variables with a probability value <0.10 were candidates for the multivariable regression model building. The final statistical model was built using a forward approach and Akaike's and Schwarz's bayesian criteria. For the Cox models, Martingale residuals were used to examine the functional form of the continuous variables. After model building, the adequacy of the proportional hazards assumption was checked. All analyses were performed using a hierarchical method to account for intercenter variability. All results were considered significant with p values <0.05. Data were analyzed with the statistical packages SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and SPSS version 21 (IBM Corporation, Armonk, New York).

RESULTS

The main baseline and procedural characteristics of the study population are shown in Table 1. A detailed comparison between patients included in the study and patients at risk with lost echocardiographic follow-up (Online Appendix) includes a comparison of study patients with patients at risk who did not have available echocardiographic follow-up at 2 years (Online Table 1).

TAVR was performed through the transfemoral approach in the majority of patients, with valves used distributed equally between balloon-expandable and self-expanding types. More than one-half of these patients were discharged with dual antiplatelet therapy; 28% received vitamin K antagonists.

All patients (n = 1,521) had an echocardiogram performed at 6 to 12 months; 625 patients had an echocardiogram at 2 years (65% of patients at risk), 258 patients at 3 years (56% of patients at risk), and 129 patients at 4 years (45% of patients at risk). The mean echocardiographic follow-up was 20 ± 13 months, and the mean clinical follow-up was 28 ± 16 months.

TABLE 1 Baseline and Procedural Characteristics (N = 1,521)

Age, yrs	81 ± 7
Female	791/1,520 (52.0)
BMI, kg/m^2	27.4 ± 5.2
Hypertension	1,271/1,517 (83.8)
Diabetes mellitus	469/1,455 (32.2)
Coronary artery disease	793/1,516 (52.3)
Cerebrovascular disease	127/831 (15.3)
COPD	415/1,508 (27.5)
CKD, eGFR <60 ml/min	758/1,507 (50.3)
Log. EuroSCORE, %	17.82 ± 12.5
Porcelain aorta	134/1,230 (10.9)
Baseline echocardiogram	
LVEF, %	55.6 ± 14.4
Peak gradient, mm Hg	74.6 ± 24.6
Mean gradient, mm Hg	45.8 ± 16.1
Aortic regurgitation	
None or trace	487/1,433 (34.0)
Mild	552/1,433 (38.5)
Moderate	277/1,433 (19.3)
Severe	117/1,433 (8.2)
Procedural approach	
Transfemoral	1221/1,518 (80.4)
Transapical or transaortic	261/1,518 (17.2)
Prosthesis type	
Edwards*	738/1,521 (48.5)
CoreValve	756/1,521 (49.7)
Others	27/1,521 (1.8)
Valve size	
≤23 mm	335/1,514 (22.1)
>23 mm	1179/1,514 (77.9)
Valve-in-valve	86/1,513 (5.7)
Discharge echocardiogram	
LVEF, %	57.3 ± 13.2
Peak gradient, mm Hg	17.2 ± 9.5
Mean gradient, mm Hg	9.9 ± 5.4
Aortic regurgitation	
None or trace	708/1,521 (46.5)
Mild	519/1,521 (34.1)
Moderate	270/1,521 (17.8)
Severe	24/1,521 (1.6)
PPM	476/1,194 (39.9)
Severe PPM	117/1,194 (9.8)
Discharge medication	
Aspirin	1234/1,506 (81.9)
Clopidogrel	1061/1,508 (70.4)
VKA	423/1,501 (28.2)

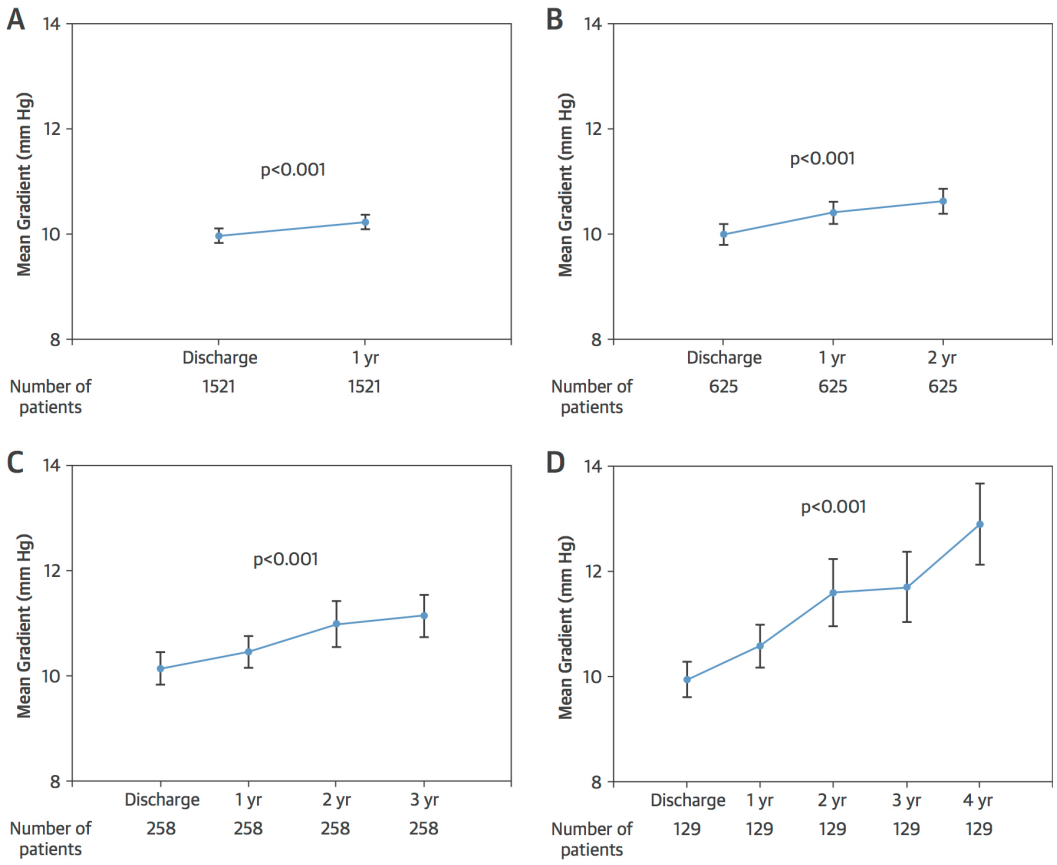
Values are mean ± SD or n/N (%). *SAPIEN and SAPIEN XT.

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PPM = prosthesis-patient mismatch; VKA = Vitamin K antagonist.

TRANSPROSTHETIC GRADIENT PROGRESSION OVER TIME. The average mean transaortic gradient decreased from 45.9 ± 16.1 mm Hg at baseline to 9.96 ± 5.37 mm Hg at discharge. The overall absolute change in transprosthetic gradient from discharge to follow-up was 0.59 ± 5.50 mm Hg (p < 0.001), and the annualized change in gradient was 0.30 ± 4.99 mm Hg/year (median: 0.00 [IQR: −1.38 to 2.00]) (Figure 1, Central Illustration).

According to univariable and multivariable analyses, the variables independently associated with increased rates of transprosthetic gradient

FIGURE 1 Progression of Mean Gradient Post-TAVR



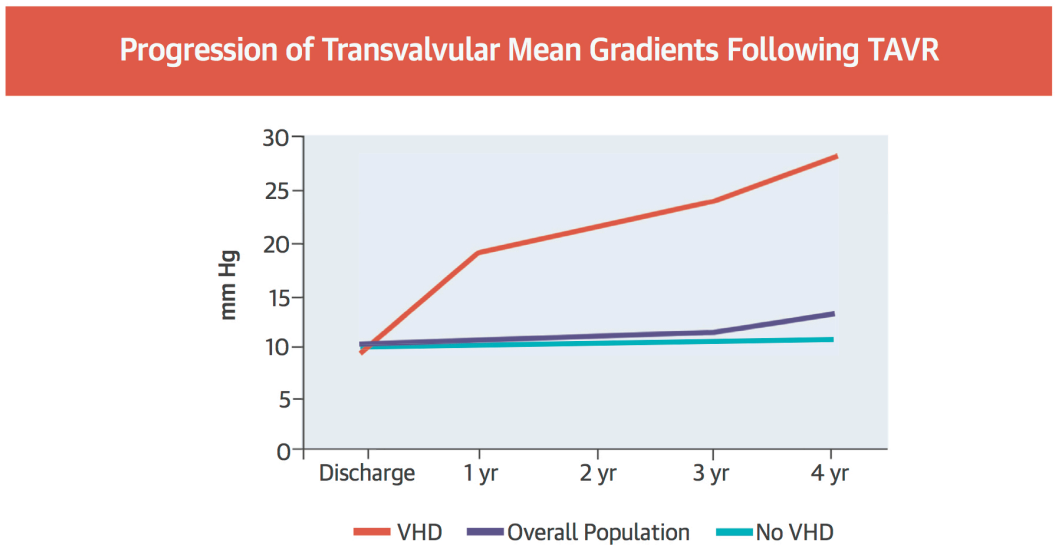
Transvalvular gradients significantly increase after transcatheter aortic valve replacement (TAVR), at 1-year **(A)**, 2-year **(B)**, 3-year **(C)**, and 4-year **(D)** follow-up.

progression over time were as follows: lack of anticoagulation therapy (β coefficient = 0.395; p = 0.009); a valve-in-valve (TAVR in a surgical bioprosthesis) procedure (β coefficient = 0.34; p = 0.036); and use of a ≤23-mm transcatheter valve (β coefficient = 0.22; p = 0.012) (Table 2).

INCIDENCE AND PREDICTORS OF VALVE HEMODYNAMIC DETERIORATION. The incidence of VHD, defined as an absolute increase in mean transprosthetic gradient ≥10 mm Hg between discharge and last follow-up, was 4.5% (overall VHD) and 2.8% within the first year (early VHD). The mean transprosthetic gradient in patients with VHD increased from 9.5 ± 5.0 mm Hg at hospital discharge to 26.1 ± 11.0 mm Hg at follow-up (p < 0.0001). Among patients meeting criteria for VHD, 47 patients (70%) had mean gradients ≥20 mm Hg at follow-up, 15 patients (22%) had gradients ≥30 mm Hg, and 8 patients (12%) had gradients ≥40 mm Hg. The main clinical and procedural characteristics of patients according to the occurrence of VHD are shown in Table 3. Patients with VHD (n = 68) were younger (p = 0.022), had a higher body mass index (BMI) (p < 0.001), were more likely to have received smaller valves (p = 0.038) and to have had valve-in-valve procedures (p = 0.008), exhibited a higher rate of PPM post-procedure (p = 0.034), and were less likely to have received anticoagulation therapy as antithrombotic treatment post-TAVR (p < 0.001).

The results of the multivariable analysis for determining VHD predictors are summarized in Table 3 and Figure 2. The independent predictors of the multivariable analysis were the absence of anticoagulation therapy at hospital discharge (p = 0.002), a valve-in-valve procedure (p = 0.032), use of a

CENTRAL ILLUSTRATION **VHD After TAVR: Progression and Predictors**



(Top) Progression of mean gradient post-transcatheter aortic valve replacement (TAVR) according to the occurrence of valve hemodynamic deterioration (VHD). **(Bottom)** Independent predictors of valve hemodynamic deterioration.

TABLE 2 **Factors Associated with Increased Transvalvular Gradient Progression**

	Univariable Analyses		Multivariable Analyses	
	β Coefficient	p Value	β Coefficient	p Value
Peak gradient at discharge, mm Hg	0.010	0.047	–	–
Valve-in-valve	0.36	0.026	0.34	0.036
23-mm THV	0.258	0.009	0.266	0.026
Severe PPM	0.388	0.014	–	–
Absence of VKA at discharge	0.199	0.031	0.370	0.026

THV = transcatheter heart valve; other abbreviations as in Table 1.

23-mm valve ($p = 0.016$), and a greater BMI ($p = 0.001$). The rates of VHD, according to these factors, are presented in Figure 3.

Among the 60 patients meeting criteria for VHD and not receiving anticoagulation therapy at the time of diagnosis, 6 patients were treated with warfarin. Of these 6 patients, 4 patients demonstrated a normalization of the mean transprosthetic gradient, and 1 failed to respond to oral anticoagulation therapy and finally underwent another TAVR procedure; the sixth patient was lost to follow-up. Another 4 patients underwent another TAVR after observation of a rising transprosthetic gradient.

Compared with the whole cohort of at-risk patients, patients with echocardiographic follow-up at

TABLE 3 Baseline and Procedural Characteristics According to VHD Occurrence

	Valve Hemodynamic Deterioration		Univariate Model		Multivariate Model	
	No VHD (n = 1,453)	VHD (n = 68)	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	81 ± 7	78 ± 9	0.97 (0.94–0.99)	0.022	–	–
Female	51.9	55.9	1.12 (0.66–1.91)	0.669	–	–
BMI, kg/m^2	27.3 ± 5.1	29.4 ± 5.9	1.08 (1.03–1.12)	<0.001	1.08 (1.03–1.13)	0.001
Hypertension	83.3	85.3	0.98 (0.49–1.94)	0.951	–	–
Dyslipidemia	65.9	80.0	1.64 (0.76–3.52)	0.208	–	–
Diabetes mellitus	31.7	42.4	1.51 (0.91–2.51)	0.110	–	–
Coronary artery disease	52.0	58.8	1.23 (0.74–2.03)	0.421	–	–
Cerebrovascular disease	14.6	10.0	0.75 (0.32–1.81)	0.527	–	–
COPD	27.6	25.0	0.87 (0.49–1.55)	0.640	–	–
CKD, eGFR <60 ml/min	50.1	54.4	0.93 (0.56–1.52)	0.757	–	–
Log. EuroSCORE, %	17.9 ± 12.6	16.5 ± 9.9	0.98 (0.96–1.00)	0.098	–	–
Porcelain aorta	10.9	10.2	0.60 (0.25–1.45)	0.254	–	–
Baseline echocardiogram						
LVEF, %	55.6 ± 14.6	54.6 ± 11.2	0.99 (0.98–1.01)	0.483	–	–
Peak gradient, mm Hg	74.6 ± 24.6	73.1 ± 24.3	1.00 (0.99–1.01)	0.757	–	–
Mean gradient, mm Hg	45.8 ± 16.1	45.9 ± 16.5	1.01 (0.99–1.02)	0.517	–	–
Moderate to severe aortic regurgitation	27.0	23.1	1.76 (0.77–4.02)	0.183	–	–
Procedural characteristics						
Balloon-expandable THV	47.7	66.2	1.94 (0.89–2.65)	0.190	–	–
≤23-mm THV	21.5	35.3	1.57 (1.03–2.42)	0.038	2.07 (1.14–3.76)	0.016
Valve-in-valve	5.3	13.2	2.74 (1.31–5.77)	0.008	2.32 (1.07–5.04)	0.032
Discharge echocardiogram variables						
LVEF, %	57.2 ± 13.2	57.4 ± 11.2	1.01 (0.99–1.03)	0.400	–	–
Peak gradient, mm Hg	19.1 ± 9.6	19.6 ± 8.4	0.99 (0.96–1.03)	0.733	–	–
Mean gradient, mm Hg	10.0 ± 5.3	9.5 ± 4.9	0.96 (0.90–1.01)	0.133	–	–
Moderate to severe aortic regurgitation	19.1	23.5	1.23 (0.29–5.27)	0.779	–	–
PPM						
Moderate to severe	39.7	55.2	1.97 (1.05–3.70)	0.034	–	–
Severe	9.4	20.0	2.63 (1.25–5.51)	0.010	–	–
Discharge medication						
Aspirin	81.6	88.2	1.28 (0.59–2.78)	0.527	–	–
Clopidogrel	70.2	73.5	1.45 (0.81–2.61)	0.210	–	–
VKA	29.0	11.8	3.16 (1.49–6.69)*	<0.001	3.17 (1.49–6.73)*	0.003
Echocardiographic follow-up, months	20 ± 13	20 ± 15	–	–	–	–

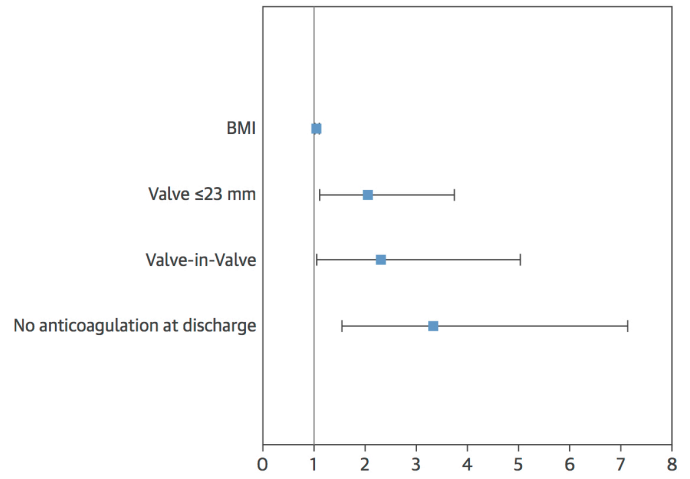
Values are mean ± SD or %, unless otherwise noted. *Absence of anticoagulation at discharge.
CI = confidence interval; HR = hazard ratio; VHD = valve hemodynamic deterioration; other abbreviations as in Tables 1 and 2.

2 years were more likely to have a previous history of SAVR and chronic kidney disease and to have a greater BMI, and they were more frequently treated with small valves (Online Table 2). Given that aortic regurgitation (AR) at discharge may influence mean gradients during follow-up, a subanalysis excluding patients with prosthesis size ≤23 mm, valve-in-valve, and AR that was moderate to severe, was conducted. In this subanalysis, the absence of anticoagulation therapy at discharge was the only independent predictor of VHD (hazard ratio [HR]: 4.58; 95% confidence interval [CI]: 1.07 to 19.57; p = 0.04) (Online Table 3).

An additional analysis was performed to evaluate the factors associated with VHD within the year after TAVR (early VHD), defined as a ≥10 mm Hg increase in mean transprosthetic gradient within the first year post-TAVR compared with discharge assessment. A total of 42 patients met criteria for early VHD. The main clinical and procedural characteristics of patients according to the occurrence of early VHD are shown in Online Table 3. In multivariate analysis, the independent predictors of early VHD were the absence of anticoagulation therapy (HR: 6.17; 95% CI: 1.87 to 20.3; p = 0.003), a valve-in-valve procedure (odds ratio [OR]: 3.61; 95% CI: 1.48 to 8.84; p = 0.005); and greater BMI (OR for each increase in 1 kg/m^2: 1.10; 95% CI: 1.04 to 1.16; p < 0.001).

Of the 42 patients presenting with early VHD, 2 underwent another TAVR procedure, and a further 4 patients were treated with warfarin. After the diagnosis of early VHD, additional echocardiography data

FIGURE 2 Predictors of Transcatheter VHD Post-TAVR



Results of the multivariate analysis show factors associated with a higher risk of transcatheter valve hemodynamic deterioration (VHD) after transcatheter aortic valve replacement (TAVR). BMI = body mass index; CI = confidence interval; HR = hazard ratio.

were available in 9 of the 36 patients who did not receive specific treatment for their VHD. No significant progression of mean transprosthetic gradients between 1 and 2 years post-TAVR were noted in these patients ($p = 0.26$) (Figure 4). A landmark analysis was conducted at 1-year follow-up to determine whether early VHD was associated with poorer clinical outcomes. There were no significant differences between the groups in death, cardiovascular death, or stroke at follow-up (Figure 5).

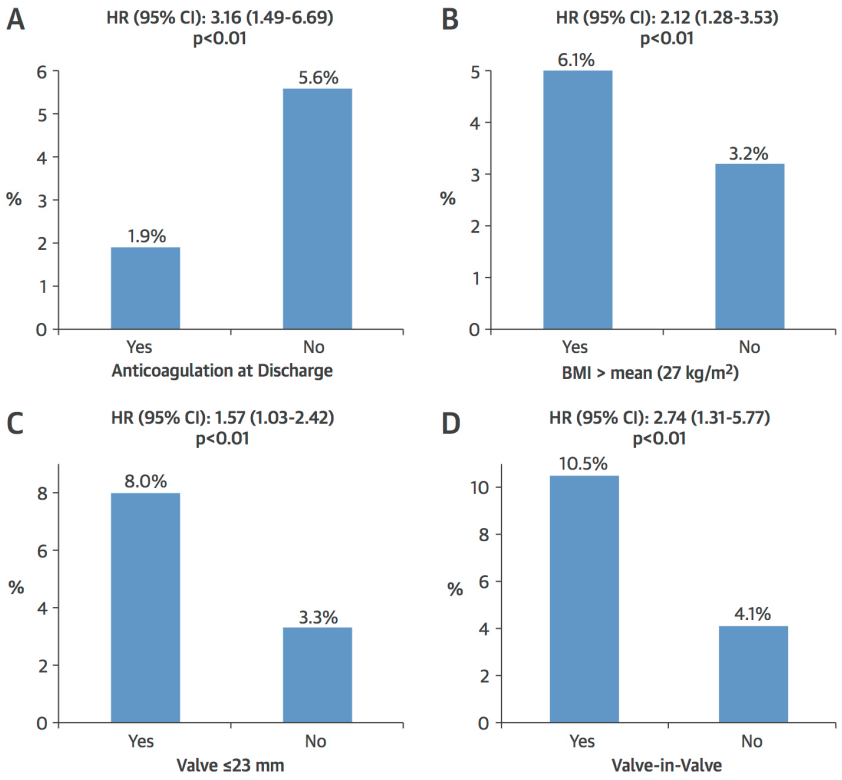
DISCUSSION

To the best of our knowledge, this is the first study systematically assessing the incidence, timing, and risk factors associated with VHD within a large TAVR cohort. The lack of anticoagulation therapy, a valve-in-valve procedure, a greater BMI, and the use of a 23-mm transcatheter heart valve (THV) were factors associated with higher rates of VHD post-TAVR. Identifying factors posing the greatest risk for incident THV deterioration is of utmost clinical relevance considering the recent rapid expansion of THV technologies, the inevitable push to treat lower-risk and younger patients with THV technologies, and the current lack of evidence-based post-TAVR antithrombotic therapeutic strategies.

THV dysfunction has yet to be systematically examined on a large-scale prospective basis. According to VARC-2 recommendations (15), assessing THV stenosis requires an integrative process using multiple measures of valve function (15). Limitations of both flow-dependent (peak aortic jet velocity and mean gradient) and flow-independent (EOA and Doppler velocity index) parameters are, however, well recognized within this consensus document. Mean transprosthetic gradients ranging from 20 to 40 mm Hg have been proposed in VARC-2 to indicate mild valve stenosis, whereas a mean gradient >40 mm Hg is considered to represent moderate to severe THV stenosis post-TAVR. In fact, most patients (70%) with VHD in our study exhibited mean gradients ≥20 mm Hg at follow-up, 22% had gradients ≥30 mm Hg, and 12% had gradients ≥40 mm Hg. However, the use of a fixed cutoff point could lead to an overdiagnosis of acquired THV stenosis in patients with elevated mean transprosthetic gradients at discharge caused by suboptimal valve sizing, positioning, or deployment or as a result of PPM. Similarly, relevant changes in valve hemodynamics over time could be underestimated in patients with low mean transprosthetic gradients at discharge (e.g., mean gradient increasing from 5 to 18 mm Hg).

Previous studies in surgical patients used an annualized change in mean gradient of >3 mm Hg/year to define SVD post-SAVR (7). Although this definition seemed appropriate in surgical cohorts with longer-term follow-up, its direct extrapolation to TAVR-treated patients with a mean follow-up of 20 months could be misleading. As proposed in a recent study (8),

FIGURE 3 Incidence of VHD According to Different Risk Factors

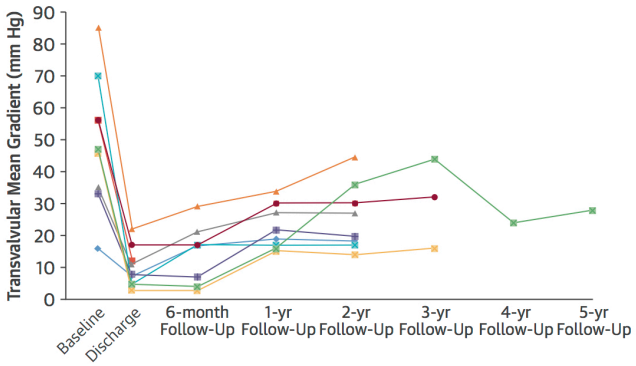


Incidence of valve hemodynamic deterioration (VHD) after transcatheter aortic valve replacement varied according to antithrombotic treatment **(A)**, body mass index (BMI) **(B)**, valve size **(C)**, and valve-in-valve procedure **(D)**. Abbreviations as in Figure 2.

we defined VHD as an absolute increase in mean transprosthetic gradient of ≥10 mm Hg over time. In an attempt to describe the process of VHD more accurately, we further calculated the annualized change in mean transprosthetic gradient. Importantly, the main determinants of VHD were also associated with greater annualized change in transprosthetic gradient, thus highlighting the consistency of these phenomena and their etiological implications.

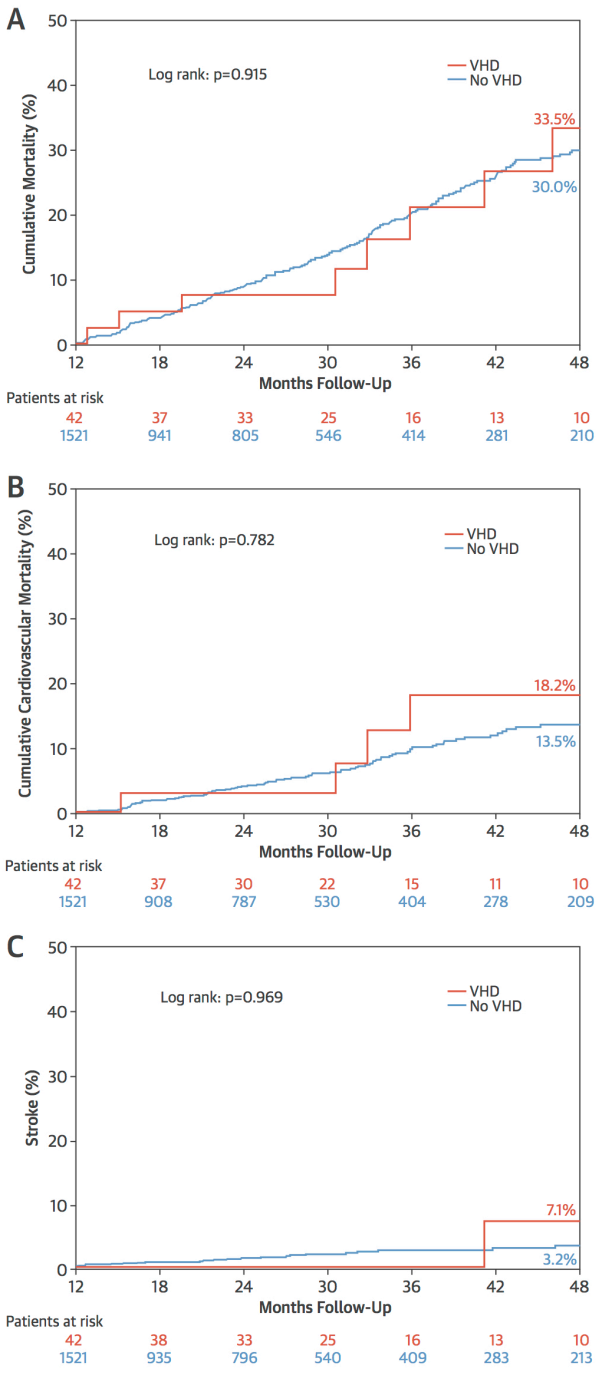
INCIDENCE OF VALVE HEMODYNAMIC DETERIORATION POST-TRANSCATHETER AORTIC VALVE REPLACEMENT. In this study, the annualized increment in mean transprosthetic gradient post-TAVR was 0.3 mm Hg/year. Some, but not all, previous studies assessing longer-term hemodynamic results post-TAVR have reported similar progression rates. In the Canadian multicenter experience (10), 339 patients were followed for a mean follow-up of 45-months, and a similar tendency of increasing gradients over

FIGURE 4 Evolution of VHD in the Absence of Specific Treatment



Changes in transvalvular gradient over time are seen in a selected group of patients (n = 9) diagnosed with valve hemodynamic deterioration (VHD) who did not receive any specific treatment for this condition.

FIGURE 5 1-Year Event Curves



At 1-year follow-up, there were no significant differences in death **(A)**, cardiovascular death **(B)**, or stroke **(C)**, between patients with or without valve hemodynamic deterioration (VHD).

time was found (from 11.4 mm Hg at discharge to 12.4 mm Hg at 3-year follow-up). Similarly, Toggweiler et al. (20) reported 5-year outcomes of 88 patients undergoing TAVR. Mean transprosthetic gradients increased, on average, by 0.27 mm Hg/year ($p = 0.06$). In this previous study, the incidence of THV failure was 3.4%, with 1 patient presenting with moderate THV stenosis. In a cohort of 70 patients who underwent balloon-expandable TAVR, Gurvitch et al. (21) reported a significant elevation in mean gradients over 3 years (from 10 mm Hg at discharge to 12.1 mm Hg after 3 years; $p = 0.03$). Ussia et al. (22) conducted a multicenter prospective study of 126 patients treated with self-expanding THVs and described similar progression rates of transprosthetic gradients (from 8.5 mm Hg at discharge to 9 mm Hg at 2-year follow-up). In contrast, no significant increases in mean THV gradient or cases of prosthetic valve failure were reported during the 5-year follow-up of the PARTNER (Placement of Aortic Transcatheter Valves) randomized trial (11) (mean gradient at discharge 10.7 mm Hg vs. 10.6 mm Hg at 5-year follow-up; $p = 0.92$). Furthermore, the 3-year follow-up of the CoreValve Italian Registry (22) reported stable THV gradients over time (mean gradient: 10.3 mm Hg at discharge and at 3-year follow-up).

We showed that increment in mean gradient is not a uniform process occurring in all patients undergoing TAVR. In our study, no significant progression of mean transprosthetic gradients was found after exclusion of the 68 patients who demonstrated overt VHD (annualized overall change in mean transprosthetic gradient was −0.2 mm Hg/year for patients without VHD). This finding implies that VHD occurs within a specific subset of patients undergoing TAVR. Among the patients who satisfied criteria for VHD, only a small proportion received specific treatment. Additionally, most patients diagnosed with VHD failed to display a continued increase in gradient beyond 1 year (**Figure 4**).

DETERMINANTS OF VALVE HEMODYNAMIC DETERIORATION POST-TRANSCATHETER AORTIC VALVE REPLACEMENT. Bioprosthetic valve thrombosis is a life-threatening but unusual complication post-SAVR, with an incidence ranging between 0.36% and 1.26%, depending on valve type (23). Both U.S. and European guidelines highlight an increased risk of valve thrombosis within 3 months post-SAVR and suggest oral anticoagulation for most patients during this period. However, the incidence and possible prevention of valve thrombosis in patients treated with TAVR have not been well established. Recently, several concerns have arisen regarding valve

thrombosis post-TAVR. In a multicenter retrospective analysis focused on THV thrombosis that included 4,266 patients, the incidence of valve thrombosis was 0.61% (n = 26) (14). Exertional dyspnea was the most common clinical presentation (65%), but up to 31% of patients had no worsening symptoms. The mean transprosthetic gradient of patients with valve thrombosis was 41 ± 14 mm Hg. Anticoagulation therapy was effective in 88% of patients, even in those without visible thrombus on echocardiography, and this therapy resulted in a significant decrease in mean gradient within 2 months. In our study, no systematic transesophageal echocardiography (TEE), computed tomography (CT), or investigation for valve thrombosis was performed; however, the higher VHD incidence in patients without anticoagulation therapy suggested thrombotic mechanism as one of the likely causes of an increasing mean gradient over time. In a current ongoing study using 4-dimensional CT (NCT02426307), the relationship between valve thrombosis and medical therapy after TAVR will be assessed. Importantly, in our study, the incidence of VHD was as low as <2% among those patients receiving anticoagulation therapy, and it increased to close to 6% in those patients treated with antiplatelet but not anticoagulant therapy. In addition, the absence of anticoagulant therapy remained an independent predictor of VHD in a subanalysis excluding patients with small valves (≤23 mm), previous SAVR (valve-in-valve procedure), and moderate to severe AR at discharge. This subanalysis supported valve thrombosis as one of the main mechanisms underlying VHD and suggested that the incidence of subclinical valve thrombosis post-TAVR may be higher than previously reported. In addition, no significant differences in clinical outcomes were observed in patients with VHD at 1-year follow-up. This finding concurred with previous studies assessing valve thrombosis post-TAVR. In a study using multidetector CT, Leetmaa et al. (24) reported that the incidence of THV thrombosis after TAVR was higher than expected; however, most patients diagnosed with THV thrombosis were asymptomatic. Despite this lack of major clinical consequences, close follow-up of such patients may be recommended because a potentially higher rate of major valve degeneration, leading to structural valve failure and clinical events, cannot be excluded. Notably, this finding may also have important implications in TAVR clinical trials. There are ongoing randomized trials evaluating the potential benefits of anticoagulation (vs. antiplatelet) therapy after TAVR. It would be important to use these trial opportunities for embedding pre-specified subanalyses of the changes in transvalvular gradients in these studies. In addition, VHD could be included as a secondary endpoint in TAVR trials.

Smaller prosthesis size was also an independent risk factor for VHD. As expected, post-implantation EOA is smaller in patients undergoing TAVR with 23-mm THVs than in those treated with >23-mm valves. Given the EOA-gradient relationship is curvilinear, a small decrease in EOA during follow-up may result in a large increase in mean gradient in the patients with a small EOA at discharge. This may explain why patients with a small valve (and thus a smaller EOA) display a larger increase in a gradient compared to patients with larger valves. Consistently, previous studies (25,26) reported that PPM was an independent predictor of surgical bioprosthesis degeneration. This finding may explain the "smaller EOA reserve" of patients with PPM. In our study, severe PPM was associated with a higher incidence of VHD on univariate analysis (p = 0.010), but it failed to reach statistical significance after adjusting for prosthesis size and other factors. Future studies are needed to evaluate the impact of PPM on post-TAVR VHD further.

Higher post-procedural mean transprosthetic gradients have been described in several valve-in-valve-TAVR series (27). Eggebrecht et al. (28) suggested that this finding could raise concerns with respect to longer-term durability of the valve-in-valve TAVR procedures and proposed close echocardiographic follow-up for detecting early signs of VHD in these patients. In the present analysis, a greater increase in mean transprosthetic gradient over time as well as a higher incidence of VHD over time were found in patients who underwent TAVR after a previous SAVR. Calcification of surgical bioprostheses is not a uniform process and occurs predominantly in the areas of the valve leaflets where mechanical stress is higher (29). Accordingly, valve-in-valve implantation could result in increased mechanical stress on the THV leaflets, as well as abnormal flow turbulences, which could promote leaflet calcification, SVD, and associated VHD. The alteration of transvalvular flow pattern by the valve-in-valve procedure could also predispose to thrombosis and thus VHD.

The present analysis also highlights the association between larger BMIs and a higher risk of incident VHD. Several studies have suggested that lipid-mediated inflammatory mechanisms may contribute to aortic bioprosthetic degeneration (6,8). Metabolic syndrome and diabetes, which are directly linked to obesity, have been associated with SVD in SAVR (7,30). These conditions may also predispose to a

higher risk of thrombosis, thereby supporting the concept that this pathological process may contribute to VHD. Unfortunately, data on lipid or inflammatory factors were not available in our study, and the role of the lipid-mediated inflammatory path in post-TAVR VHD will need to be determined in future studies.

STUDY LIMITATIONS. This study is a retrospective analysis of prospectively collected data. Only patients who survived 6 months post-TAVR were included in the present analysis; thus, our data may have underestimated actual VHD incidence. Gradient assessment was made on the basis of the results of transthoracic echocardiograms analyzed and reported by each center. There was no independent echocardiographic core laboratory analysis in this study. Only echocardiographic examinations from patients with complete serial echocardiographic follow-up examinations were analyzed. This strict criterion for echocardiographic evaluation led to a decrease in the number of echocardiographic examinations available for analysis (at 2-year follow-up, 36% of patients had missing echocardiography data), and this may have influenced the results. The measures of EOA were missing in a significant number of patients; therefore, this parameter was not used to assess VHD. Data on stroke volume, heart rate, and hemoglobin at the time of different echocardiograms were not available for most patients, and these factors may have influenced mean gradient. Furthermore, systematic TEE or CT studies were not systematically performed in patients meeting criteria for VHD, to seek the underlying process (i.e., SVD, thrombosis, pannus) of the apparent VHD further. However, recent reports have outlined the limited sensitivity of both TEE and CT to detect valve thrombosis (13,24). Marked increases in gradients on TTE post-TAVR invariably imply the possibility of valve thrombosis necessitating empirical oral anticoagulation, which is often effective at reducing transprosthetic gradients (14,31). Additionally, the need for and the nature of treatment for VHD were empirically determined at each participating center, and no systematic follow-up after diagnosis of VHD was undertaken.

CONCLUSIONS

There was a mild but significant increase in transvalvular gradients over time after TAVR. In this large series, 4.5% of patients had a significant VHD during a mean follow-up of approximately 2 years, and 2.8% of patients had experienced VHD within the first year post-TAVR. Lack of anticoagulation therapy, use of a smaller valve, a valve-in-valve procedure, and greater BMI were associated with increased risk of VHD. These findings suggest the need for closer clinical and echocardiographic follow-up in patients with such characteristics. In addition, future large-scale, prospective studies involving centralized, standardized echocardiographic core laboratory and events adjudication are required to identify whether a specific antithrombotic regimen post-TAVR could reduce the risk of incident VHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients who have undergone TAVR are prone to progressively increasing transvalvular pressure gradients over time. Factors associated with hemodynamic deterioration include greater BMI, smaller valve diameter, a valve-in-valve procedure, and lack of anticoagulation.

TRANSLATIONAL OUTLOOK: Future studies should quantify the impact of early hemodynamic deterioration and compare the effects of different antithrombotic regimens on long-term clinical outcomes after TAVR.

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KEY WORDS anticoagulation therapy, transcatheter aortic valve replacement, valve degeneration, valve-in-valve

APPENDIX For supplemental tables, please see the online version of this article.

Artículo III: "Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction."

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Transcatheter Valve-in-Valve and Valve-in-Ring for Treating Aortic and Mitral Surgical Prosthetic Dysfunction

Jean-Michel Paradis, MD, Maria Del Trigo, MD, Rishi Puri, MBBS, PhD, Josep Rodés-Cabau, MD

ABSTRACT

Bioprosthetic valve use has increased significantly. Considering their limited durability, there will remain an ongoing clinical need for repairing or replacing these prostheses in the future. The current standard of care for treating bioprosthetic valve degeneration involves redo open-heart surgery. However, repeat cardiac surgery may be associated with significant morbidity and mortality. With the rapid evolution of transcatheter heart valve therapies, the feasibility and safety of implanting a transcatheter heart valve within a failed tissue valve has been established. We review the historical perspective of transcatheter valve-in-valve therapy, as well as the main procedural challenges and clinical outcomes associated with this new less invasive treatment option. (J Am Coll Cardiol 2015;66:2019–37) © 2015 by the American College of Cardiology Foundation.

Approximately 85,000 heart valve prostheses are implanted in the United States each year, and a total of 275,000 worldwide (1). There are 2 main types of heart valve prostheses: 1) mechanical prosthetic valves, which require lifelong anticoagulation; and 2) tissue valves, which obviate the need for anticoagulation, but do not last as long as their mechanical counterparts. In the United States, the use of bioprosthetic aortic valve replacement increased from 26.7% in 1998 to 50.2% in 2005 (1,2). This major shift in the use of surgical bioprostheses, combined with their shorter durability and the increasing life expectancy of an aging population, is expected to translate into a major increase in the incidence of patients with surgical valve failure in the coming years.

The standard of care for degenerated bioprosthetic valves currently involves reoperative valve replacement. Over the last 2 decades, the mortality associated with redo aortic valve surgery has decreased significantly (3–5). Nevertheless, depending on risk factors and patient status, the recognized mortality of bioprosthetic re-replacement for structural valve failure still ranges from 3% to 23% in most series (3,6). Advanced age, female sex, preoperative New York Heart Association functional class, left ventricular dysfunction, renal failure, pulmonary disease, cognitive impairment, number of prior operations, urgency of operation, and technical difficulties caused by adhesions have each been identified as predictors of higher reoperative risk (4,5,7).

Transcatheter aortic valve replacement (TAVR) is now established as the preferred treatment option for inoperable patients and a valid alternative for high-risk individuals with severe symptomatic native aortic stenosis (8). In recent years, following rapid evolution within the transcatheter valve field, the successful placement of new bioprosthetic valves via a transcatheter approach within degenerative aortic, mitral, tricuspid, and pulmonic surgical bioprostheses has been confirmed (9–13). This study reviews the historical perspective, technical challenges, major

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

LVOT = left ventricular outflow tract

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

SHV = surgical heart valve

STS = Society of Thoracic Surgeons

SVD = structural valve deterioration

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

risks, and outcomes associated with transcatheter valve-in-valve procedures in patients with failed left-sided (aortic and mitral) surgical bioprostheses.

SURGICAL BIOPROSTHETIC VALVES

Characteristics of the main surgical bioprostheses are summarized in **Table 1**. Surgical bioprostheses are usually made of leaflets from bovine pericardium or porcine valve leaflets. Homografts, which are less frequently used, are composed of human tissue. Bioprosthetic valves can be further categorized as stented or stentless. The 3 main components of stented bioprosthetic valves are: 1) valve leaflets, which can be mounted internally or externally; 2) the stent frame, which is composed of polymeric material or alloys; and 3) a circular or scallop-shaped external sewing ring (**Figure 1**) (7). Surgical heart valves are manufactured as either intra-annular or supra-annular, and the portion visible on fluoroscopy can be either the stent frame or the sewing ring. The sewing ring is located at the bottom or 3 to 5 mm above the bottom of the stent frame in the supra- and intra-annular valve designs, respectively (14).

Stentless valves were developed to optimize the effective orifice area and thus facilitate left ventricular mass regression (15). These valves do not have a base ring or a frame to support the leaflets, are sutured to the root in the actual position of the native valve, and can be of autograft, heterograft, or homograft origin (15,16).

More recently, sutureless valves that avoid the placement of sutures following annulus decalcification have been introduced, with the objective of reducing cross-clamp and cardiopulmonary bypass duration, and facilitating minimally invasive surgery and complex cardiac interventions (17).

LABELING OF SURGICAL BIOPROSTHETIC VALVES. Surgical heart valve (SHV) sizing across manufacturers lacks standardization (18). This may lead to confusion because the valve size labeling may correspond to internal or external diameters for stented valves, and to external diameter for stentless valves (7). Consequently, 2 bioprostheses may have distinctive internal and external sewing ring diameters, despite having the same label size. For valve-in-valve therapy, the most relevant parameter relates to valve internal dimensions, which are often significantly smaller than the labeled valve size. Therefore, when envisioning a valve-in-valve procedure, it is imperative for the heart team to elicit the precise diameters of the failing bioprosthetic valve (usually available by reviewing published detailed tables providing valves dimensions (7,19) or by consulting directly with the manufacturer). However, it is important to realize that, by convention, the stent internal diameter represents exclusively the internal dimension of a bare stent covered with fabric or pericardium, without accounting for the effect of artificial leaflets sutured within the stent (20). Indeed, in a study conceived to assess the effect of tissue leaflets on stent internal diameter, the true internal valve diameter was smaller than the actual stent internal diameter in the majority of SHV designs (20). Moreover, calcification or pannus can generate a discrepancy between the expected and the observed internal stent diameters. Multidetector computed tomography (MDCT) and transesophageal echocardiography could be performed to determine the precise dimensions of the SHV. Nevertheless, considering the absence of standardized measures regarding the internal diameter of a variety of SHVs and the variability of the measurements obtained from differing imaging modalities, the exact role of pre-procedural imaging with MDCT or transesophageal echocardiogram (TEE) in the valve-in-valve field is yet to be determined.

FAILURE OF BIOPROSTHETIC VALVES: MECHANISMS AND INCIDENCE. Structural dysfunction, due to progressive tissue deterioration, is the main cause of bioprosthetic valve failure. The major pathophysiological mechanism underlying this process is cusp calcification. This mineralization process may engender pure stenosis via cusp stiffening, and may also precipitate regurgitation due to secondary tears. Recent studies have suggested that bioprosthetic valve calcification is an active rather than a passive process, and is modulated by numerous mechanisms, including lipid-mediated inflammation, immune response, and dysfunctional phosphocalcific metabolism (21). Calcium deposits can be located on cuspal tissue (intrinsic calcification), but may also develop in thrombi or endocarditic vegetations (extrinsic calcification) (1). To attenuate calcification and further degeneration, glutaraldehyde valve leaflet pretreatment is widely used.

Another mechanism contributing to the limited lifespan of bioprosthetic valves is progressive collagen deterioration (1). Design-related tearing, rather than leaflet calcification, generally explains the deterioration of bovine pericardial valves (1). The formation of tissue overgrowth (e.g., pannus), thrombus, or paravalvular leaks can usually explain bioprosthesis dysfunction not related to leaflet failure. Usually, valve stenosis is the consequence of calcification, pannus, or thrombus, whereas leaflet destruction or

paravalvular leak will lead to regurgitation. The outcome of the degenerative tissue valves can also be a combination of stenosis and regurgitation.

The mechanisms of aortic bioprosthetic dysfunction are equally distributed as predominantly stenotic, regurgitant, or mixed, with a higher rate of stenotic dysfunction among stented and smaller (≤21 mm) valves, and a predominant regurgitant mechanism among stentless valves (11). In mitral bioprostheses, regurgitation is the predominant mechanism of valve dysfunction (49%), followed by stenosis (21%) and combined mechanisms (30%) (22).

The incidence of aortic and mitral bioprosthesis structural valve deterioration (SVD) requiring reintervention is 20% to 30% at 10 years and over 50% at 15 years (23,24) (**Central Illustration**). Because bioprosthetic valve calcification is hastened in younger individuals, the likelihood of primary tissue failure diminishes with age (1,25,26) (**Figure 2**). Sénage et al. (27) showed that early valve failure is not infrequent and constitutes a life-threatening condition. A younger age at implantation, renal failure, hyperparathyroidism, higher post-operative gradients, prosthesis-patient mismatch (PPM), and mitral valve position are associated with a higher risk of tissue valve deterioration (21,23,24,26). One of the most likely hypotheses for the greater frequency of mitral bioprosthetic failure relative to aortic bioprosthetic failure may be partially related to the higher close-off pressure in the mitral position (usually >100 mm Hg vs. <100 mm Hg in the aortic position). Also, the closure time is expected to be greater with a mitral prosthesis compared with an aortic prosthesis, possibly contributing to a higher degeneration rate (1).

TRANSCATHETER VALVE-IN-VALVE INTERVENTIONS: HISTORICAL PERSPECTIVES

AORTIC POSITION. Following pre-clinical studies evaluating the valve-in-valve technique, the first-in-human cases of valve-in-valve procedures for treating aortic bioprosthetic dysfunction were reported in 2007 using the CoreValve and Cribier-Edwards valve systems (9,28,29). This was followed by publication of several case reports of valve-in-valve procedures combining different transcatheter devices (30–35) and surgical valves, as well as several small single-center and multicenter series (36–39). More recently, retrospective collection of valve-in-valve cases on a voluntary basis from different centers worldwide has led to the publication of the 2 largest series of valve-in-valve procedures to date, including 202 and 459 patients, respectively (10,11). In addition, a prospective registry evaluating the Edwards SAPIEN valve for valve-in-valve procedures has recently been completed (PARTNER VinV registry [PARTNER II Trial: Placement of AoRTic TraNscathetER Valves]; NCT01314313) and another prospective registry using the CoreValve system (Medtronic) is still ongoing (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis With Significant Comorbidities in Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01675440).

To date, the vast majority of valve-in-valve procedures for aortic valve dysfunction have been performed with the Edwards SAPIEN/SAPIEN XT valves (Edwards Lifesciences, Irvine, California) and the CoreValve system (Medtronic, Minneapolis, Minnesota). Nonetheless, most transcatheter valves available for the treatment of native aortic valve stenosis have also been used for treating surgical aortic bioprosthetic dysfunction (**Figure 3**).

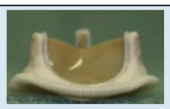
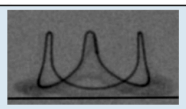
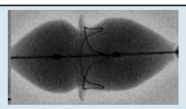
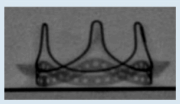
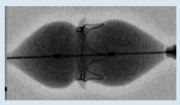
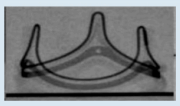
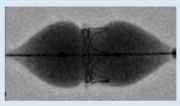
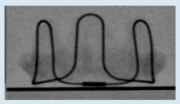
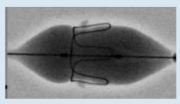
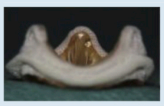
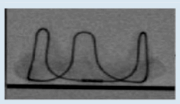
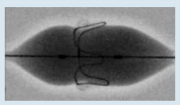
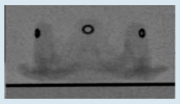
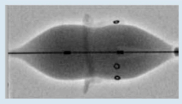
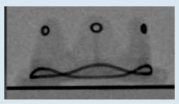
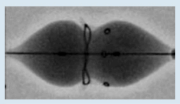
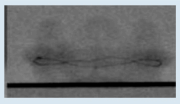
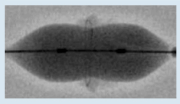
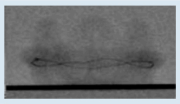
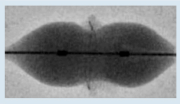
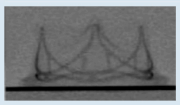
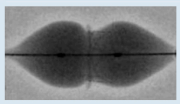
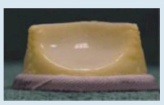
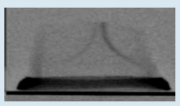
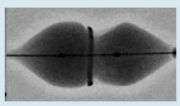
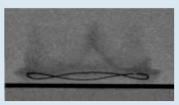
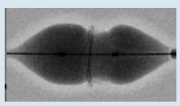
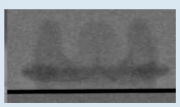
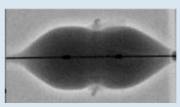
MITRAL POSITION. Data from pre-clinical studies proving the concept of mitral valve-in-valve and valve-in-ring procedures were reported in 2007 (9) and 2009 (40), respectively. The first-in-human cases of valve-in-valve and valve-in-ring procedures for mitral valve or ring dysfunction were reported in 2009 (41) and 2011 (42), respectively. Most cases of mitral valve-in-valve or valve-in-ring have been performed with the balloon-expandable Edwards system, via transapical or antegrade transfemoral approaches. The balloon-expandable Melody valve (Medtronic, Minneapolis, Minnesota) has been used in a minority of cases (43,44). More recently, the use of self-expandable transcatheter valve systems for treating mitral valve dysfunction has also been reported (45) (**Figure 3**).

AORTIC VALVE-IN-VALVE PROCEDURES

PRE-PROCEDURAL WORK-UP AND PROCEDURAL ASPECTS. The pre-procedural work-up and periprocedural steps involved in valve-in-valve procedures are similar to those used for patients with native aortic valve stenosis considered for TAVR (46). However, specific aspects of preparation of a valve-in-valve procedure should be considered:

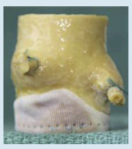
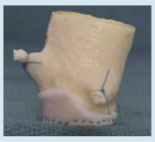
1. *Type of bioprosthesis dysfunction.* A sound knowledge of prior cardiac surgery and failed bioprosthetic valves is essential. A meticulous echocardiographic evaluation is very useful for determining the mode of valve failure. In order to eliminate endocarditis or paravalvular (rather than

TABLE 1 Main Characteristics of SHVs

Manufacturer	Valve Model	SHV Image	Leaflet Tissue	Relationship of Leaflets to the Stent Frame	SHV Fluoroscopic Image	Neoannulus Fluoroscopic Image
			Stented SHV			
Edwards Lifesciences (Irvine, California)	Carpentier-Edwards Perimount 2700		Bovine Pericardium	Inside		
	Carpentier-Edwards Perimount		Bovine Pericardium	Inside		
	Carpentier-Edwards Perimount Magna and Magna ease		Bovine Pericardium	Inside		
	Carpentier-Edwards aortic porcine bioprosthesis		Porcine	Inside		
	Carpentier-Edwards supra-annular aortic porcine bioprosthesis		Porcine	Inside		
Medtronic (Minneapolis, Minnesota)	Mosaic Tissue valve		Porcine	Inside		
	Hancock II Tissue valve		Porcine	Inside		
St. Jude Medical (St. Paul, Minnesota)	Epic (Biocor) valve		Porcine	Inside		
	Epic Supra (Biocor Supra) valve		Porcine	Inside		
	Trifecta		Bovine Pericardium	Outside		
Sorin (Milan, Italy)	Mitroflow		Bovine Pericardium	Outside		
	Soprano Armonia		Bovine Pericardium	Inside		
Vascutek (Inchinnan, United Kingdom)	Aspire		Porcine	Inside		

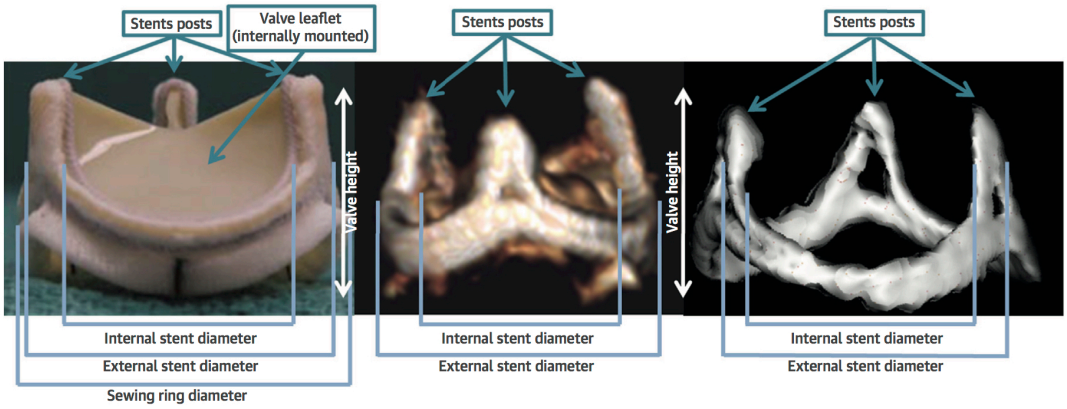
Continued on the next page

TABLE 1 Continued

Manufacturer	Valve Model	SHV Image	Leaflet Tissue	Relationship of Leaflets to the Stent Frame	SHV Fluoroscopic Image	Neoannulus Fluoroscopic Image
		Stentless SHV				
Edwards Lifesciences	Prima root		Porcine root	Inside		
Medtronic	Freestyle root		Porcine root	Inside		
St. Jude Medical	Toronto SPV root		Porcine root	Inside		
Sorin	Freedom Pericarbon		Bovine Pericardium	Inside		
		Sutureless SHV				
Edwards Lifesciences	Intuity Elite		Bovine Pericardium	Inside		
Medtronic	3F Enable		Equine Pericardium	Inside		
Sorin	Perceval S		Bovine Pericardium	Inside		
Arbor Surgical Technologies Inc. (Irvine, California)	Trilogy		Bovine Pericardium	Inside		

Adapted with permission from Bapat et al. (19), Bapat et al. (55), and Flameng et al. (81).
SHV = surgical heart valve.

FIGURE 1 Dimensions and Design Characteristics of a Stented Bioprosthetic Valve



(Left) Carpentier-Edwards Perimount Magna Ease aortic valve (Edwards Lifesciences, Irvine, California). **(Middle, Right)** Computed tomography images of the Carpentier-Edwards Perimount Magna Ease aortic valve.

transvalvular) leaks, TEE should be routinely performed in patients with regurgitation as the main mode of valve failure. For those patients presenting predominantly with valve stenosis, a careful review of prior echocardiographic examinations, as well as recent changes in clinical status should be undertaken to differentiate between surgical valve failure and PPM following surgical aortic valve replacement (SAVR). This is of particular importance in those patients with smaller surgical valves (≤21 mm), which are frequently associated with higher transvalvular gradients and a greater incidence of moderate-to-severe PPM post-SAVR (47). At best, a valve-in-valve procedure is expected to reduce transvalvular gradients to the values obtained immediately following SAVR, and this should be taken into account in the clinical decision-making process for valve-in-valve procedures.

2. *Valve sizing* remains a challenging aspect of valve-in-valve procedures. As previously discussed, a detailed knowledge of the surgical valve labeling is essential. Importantly, the true inner diameter of the surgical valve, which is usually a few millimeters smaller than the outer diameter, is used for sizing purposes. As transcatheter valves are sutureless devices, ensuring transcatheter valve fixation and stability greatly depends on the principle of relative oversizing of the transcatheter valve with respect to aortic annulus dimensions. Whereas significant paravalvular regurgitation or embolization may result from transcatheter valve undersizing, excessive oversizing can lead to incomplete expansion, incorrect functioning, and/or higher residual gradients (20). To date, in the absence of dedicated sizing guidelines for valve-in-valve procedures, the main principles of sizing (including the degree of oversizing) used for native aortic valves are usually applied (48–50). Thus, performing a 3-dimensional (3D) reconstruction (by computed tomography [CT] or TEE) of the surgical prosthesis in order to obtain an additional measure of the inner diameter and area/perimeter is advisable. Three-dimensional TEE, a technique that can be used intraprocedurally during TAVR and does not require iodinated contrast, has superior temporal resolution, provides physiological information, and essentially eliminates motion-based artifacts. Nonetheless, 3D TEE is hampered by suboptimal lateral resolution in the coronal plane, which diminishes the ability to measure the blood/tissue interface in this plane. In contrast, MDCT, which requires iodinated contrast, typically offers superior tissue/lumen contrast, but may be limited by artifacts because of partial volume-averaging effects (blooming), heart/lung motion, patient motion, and arrhythmias. Both imaging modalities are user-dependent, and prime image acquisition and analysis are essential for satisfactory annular assessment. Indeed, echocardiography and MDCT are often considered complementary imaging modalities.

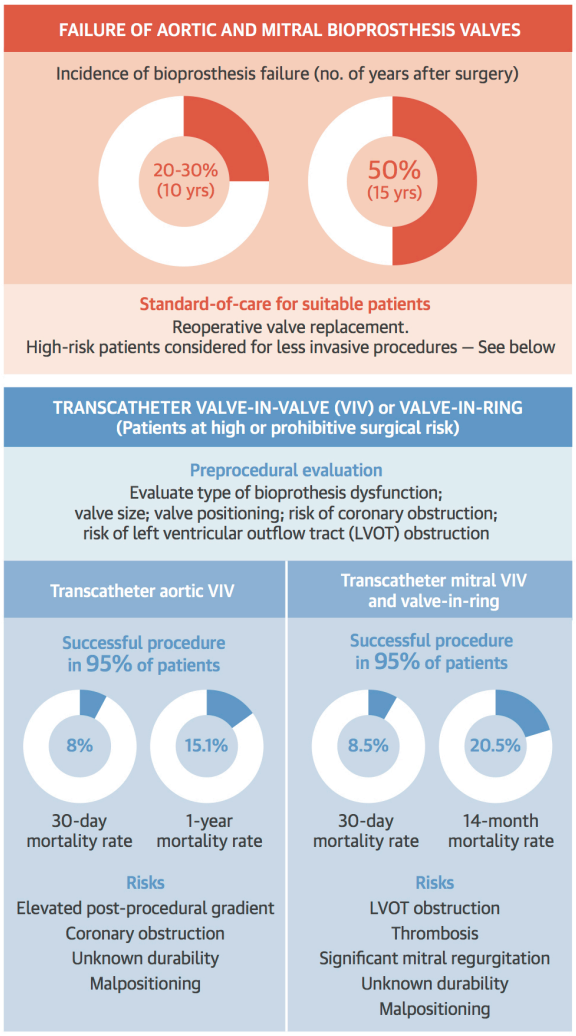
In addition to those imaging modalities, the use of the *Valve in Valve app* is highly recommended. This free app, developed collaboratively by the technology

company UBQO and Dr. Vinayak Bapat, provides specific information according to different clinical scenarios and is helpful for the preparation of valve-in-valve procedures.

3. *Risk of coronary obstruction.* Aortic valve-in-valve procedures have been associated with an increased risk of coronary obstruction, especially in patients with stentless valve dysfunction. In a large series of coronary obstruction cases post-TAVR, the risk of coronary obstruction was >2 times more frequent among valve-in-valve procedures compared with TAVR performed within native valves (51). The main anatomic factors associated with a higher risk of coronary obstruction were low coronary height (<12 mm) and reduced diameter of the sinus of Valsalva (<30 mm). During valve-in-valve cases, a leaflet directly contacting either the coronary ostium, or the aortic root surrounding the coronary ostium most commonly generates coronary obstruction. The major predisposing condition is the proximity of the coronary ostium to the projected final position of the displaced bioprosthetic leaflet after transcatheter heart valve (THV) placement. Therefore, during the pre-procedural work-up, it is often useful to perform aortography to identify patients at risk for coronary obstruction. This should be done in a projection perpendicular to both the SHV and the coronary ostia. Because coronary ostia are typically located midway between 2 surgical valve posts, a projection perpendicular to the coronary ostia is generally attained by perfectly superimposing 2 adjacent posts (1 to 2 technique) (52). Computed tomography or 3D TEE, by allowing 3D anatomic assessment, can also be used in the screening process for the risk of coronary obstruction. However, even if these modalities can assess the geometric axis of the SHV at the level of the coronary artery ostia and can anatomically define the distance between the future THV and the coronary ostia, their role in predicting this potential life-threatening complication is still evolving. When a patient is at high risk of coronary obstruction, the following options should be contemplated: consider redo open heart surgery; use of periprocedural general anesthesia; selection of a smaller or underfilled transcatheter valve; positioning the transcatheter valve in a lower position with respect to the SHV; use of a retrievable device (e.g., Evolut-R, Portico, Lotus); use of a trancatheter valve with clipping mechanism that grasp SHV leaflets (e.g., JenaValve, Engager); and placement of a wire and an undeployed stent within the distal coronary bed, ready to be pulled back and implanted emergently, if needed (52).

4. *Need for balloon pre-dilation.* The role of balloon aortic pre-dilation during valve-in-valve procedures is debatable. Degenerative bioprotheses

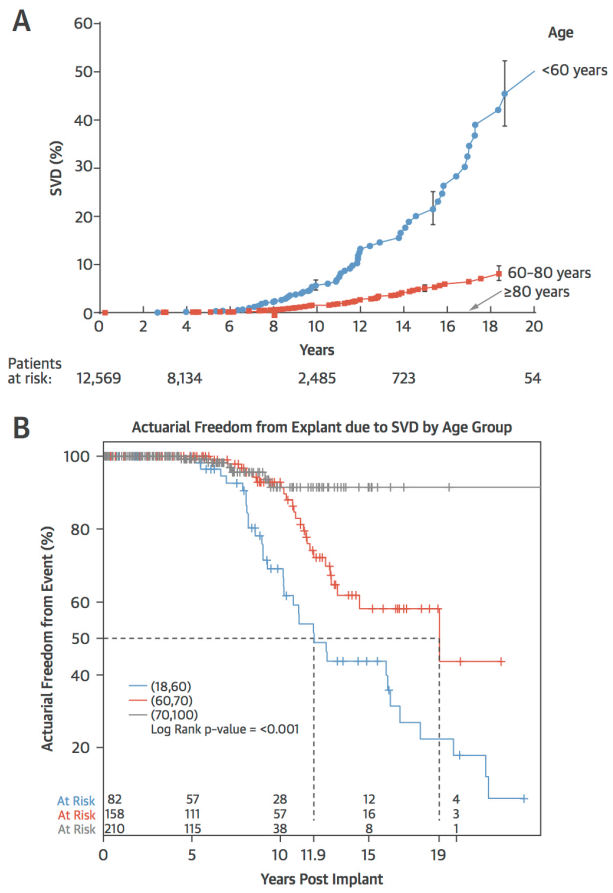
CENTRAL ILLUSTRATION **Valve-in-Valve: Failure of Bioprosthesis Valves and Transcatheter Options for High-Risk Patients**



Paradis, J-.M. et al. J Am Coll Cardiol. 2015; 66(18):2019-37.

Incidence of bioprosthesis valve dysfunction and transcatheter aortic valve-in-valve and valve-in-ring as alternative treatments in those patients at high or prohibitive surgical risk. Aspects of the main pre-procedural evaluation, risks, and results of transcatheter treatment of aortic and mitral bioprosthesis dysfunction are shown.

FIGURE 2 Rates of Reintervention Over Time in Aortic and Mitral Surgical Bioprostheses

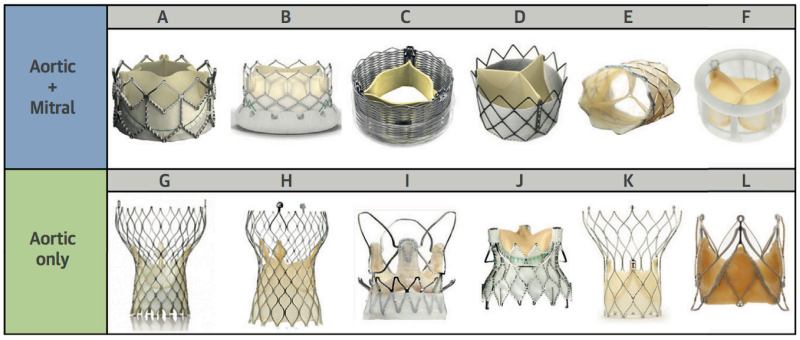


(A) Age and probability of explant owing to structural valve deterioration (SVD) of aortic bioprosthetic surgical heart valves. Patients are grouped according to age range. Adapted with permission from Johnston et al. (26). **(B)** Actuarial freedom from explant because of SVD of bioprosthetic mitral surgical heart valves, stratified by age groups. Adapted with permission from Bourguignon et al. (80).

are friable, and the risks of embolization and stroke or destruction and acute regurgitation with pre-dilation must be weighed against the possibilities of both difficultly in crossing a severely stenotic surgical valve and suboptimal expansion of the THV. Although societal guidelines advise against using balloon dilation for prosthetic left-sided heart valves (53,54), balloon pre-dilation is still performed in about one-fourth of valve-in-valve cases (11). When a retrograde approach is selected (e.g., transarterial or transaortic crossing of an aortic biosprosthesis), cautious pre-dilation with an undersized balloon may be considered, especially in the presence of a bulky and severely calcified stenotic aortic valve. In those cases performed through a transapical approach or in the presence of regurgitant bioprostheses, pre-dilation is generally not recommended. In surgical valves with no fluoroscopic markers or in a Mosaic valve, balloon pre-dilation could be used to locate the exact level of the neoannulus and facilitate transcatheter valve positioning. Finally, balloon pre-dilation can contribute to the evaluation of the geometric relationship between the SHV and the coronary ostia (52).

5. *Transcatheter valve positioning.* The optimal placement of a transcatheter valve inside a SHV can be defined as a placement where the valve is securely fixed to avoid embolization, with its uncovered portion remaining above the sewing ring of the SHV (14). The use of a reference plane, or "neo-annulus" has been proposed by Bapat et al. (55) to achieve an optimal placement of THV devices inside a given surgical heart valve (**Table 1**). Indeed, irrespective of the valve design, the narrowest portion of all surgical valves is at the level of its sewing ring, which should be used as a reference level during valve-in-valve cases (55). The relationship between the fluoroscopically visible component of a SHV and the level of the sewing ring must be well acknowledged to optimize transcatheter valve positioning within any SHV. Similar to conventional TAVR, finding a fluoroscopic coplanar or perpendicular view to the bioprosthetic annular plane is helpful. This can be accomplished by finding a fluoroscopic angulation where the radiopaque components of the bioprosthetic basal ring appear as a straight line or the radiopaque components of the valve posts seem to be at the same height (52). The use of TEE can be very useful for valve positioning in the absence of surgical valve leaflet calcification, in the presence of stentless valves, or when the mode of SHV failure is severe regurgitation. Rapid ventricular pacing and the use of repositionable self-expanding devices can also be considered to obtain a perfect depth of implantation. Ideally, the Edwards SAPIEN XT valve should be implanted 4 to 5 mm below the sewing ring of the SHV, whereas the CoreValve should be positioned 5 mm below the neoannular plane (14). Interestingly, optimal THV positioning within stented SHVs can usually be obtained with minimal contrast dye injection, or even without any. Several examples of aortic valve-in-valve cases are shown in **Figure 4**.

FIGURE 3 Transcatheter Valves Used for Valve-in-Valve Procedures



(A) Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California); **(B)** SAPIEN 3 (Edwards Lifesciences, Irvine, California); **(C)** Lotus (Boston Scientific Inc, Natick, Massachusetts); **(D)** Inovare valve (Braile Biomedica Inc, São José do Rio Preto, Brazil); **(E)** Melody (Medtronic, Minneapolis, Minnesota); **(F)** Direct Flow (Direct Flow Medical Inc, Santa Rosa, California); **(G)** CoreValve (Medtronic, Minneapolis, Minnesota); **(H)** Evolut R (Medtronic, Minneapolis, Minnesota); **(I)** Acurate TA system (Symetis Inc, Écublens, Switzerland); **(J)** Engager (Medtronic, Minneapolis, Minnesota); **(K)** Portico (St. Jude Medical Inc., St. Paul, Minnesota); **(L)** JenaValve (JenaValve Inc, Munich, Germany). Valves **A** to **F** have been used for both aortic and mitral valve-in-valve procedures. Valves **G** to **L** have been used only for aortic valve-in-valve cases.

EARLY OUTCOMES

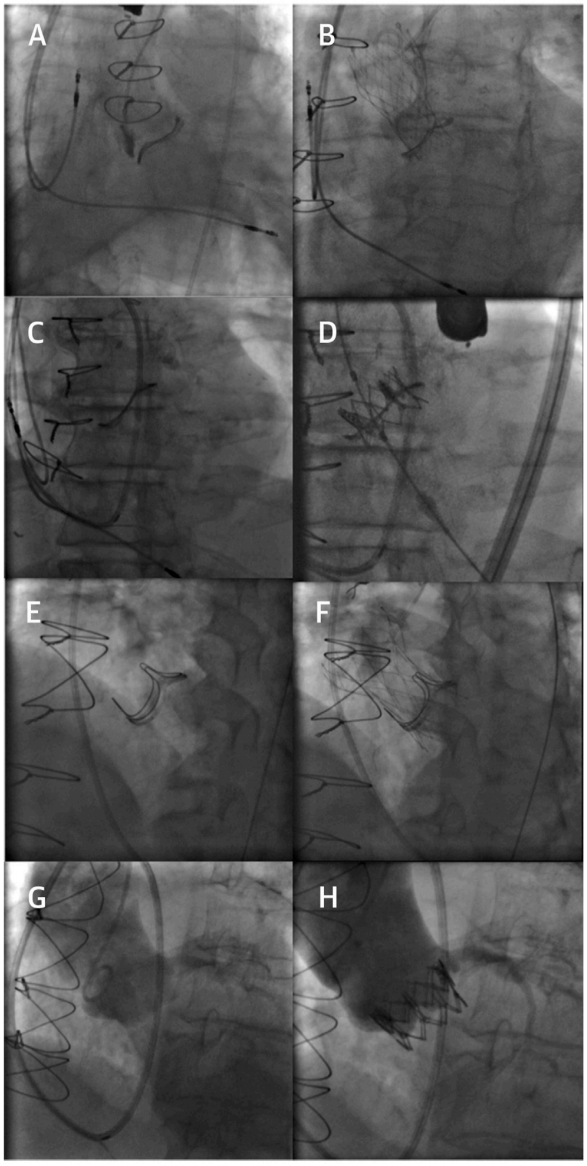
PROCEDURAL AND 30-DAY OUTCOMES. Baseline characteristics and outcomes of all published case series including more than 10 aortic valve-in-valve procedures are shown in **Table 2** (10,34,36,56-66). The mean age was 78 years, and 58% of patients were men. The mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and Society of Thoracic Surgeons (STS) score were 31.3% and 11.3%, respectively, which represented a much higher risk profile than those reported in most TAVR within native valve series (8). Most surgical valves were stented (82% vs. 18% stentless). The selected routes were transfemoral, transapical, transaxillary, transaortic, and subclavian in 55%, 41.6%, 2%, 1%, and 0.3% of patients, respectively.

The transcatheter valve was successfully implanted in 94.7% of patients, and the mean 30-day mortality rate was 8% (**Central Illustration**). The mean rate of periprocedural complications was: valve malpositioning/embolization (12.4%); stroke (1.4%); pacemaker implantation (7.6%); and coronary obstruction (2.2%). Interestingly, although the rate of coronary obstruction and valve malpositioning seems to be higher, as compared with TAVR within native valves, pacemaker implantation rates are much lower. We hypothesize that the surgical valve structure may function as a protective factor in such cases, in addition to a higher (more aortic) implantation of the THV. The relatively high malpositioning rate may be due to positioning challenges in those cases with aortic regurgitation as a predominant mechanism of valve failure, which indeed are frequently associated with a lower degree of valve calcification. Also, the lack of fluoroscopic markers in some stentless valves can make the final positioning of the transcatheter valve challenging, and this may translate into a higher rate of valve malpositioning.

VALVE HEMODYNAMICS. The mean transvalvular gradient after aortic valve-in-valve procedures was 15.5 mm Hg (>10 mm Hg in most patients), which is higher than the gradients reported following TAVR within native valves (usually ≤10 mm Hg) (8,46). The global rate of severe PPM (defined as an effective orifice area <0.65 cm^2/m^2) following aortic valve-in-valve is 32.1% (**Figure 5**). That the transcatheter valves are implanted in a nondistensible structure and the amount of material occupying the aortic annulus space (surgical valve + transcatheter valve) may partially explain such results. In addition, some patients already presented with elevated gradients and moderate-to-severe PPM following SAVR (particularly in the group of smaller surgical valves) (47), and this also contributes to the high rate of elevated transvalvular gradients following valve-in-valve procedures.

Dvir et al. (10) evaluated the factors associated with higher transvalvular gradients following valve-in-valve procedures. The use of a balloon-expandable valve (particularly in those patients with surgical valves ≤23 mm) and stenosis (instead of

FIGURE 4 Examples of Aortic Valve-in-Valve Cases



(A) Pre-procedural fluoroscopic image of a failing 21-mm Sorin Mitroflow surgical heart valve (SHV) (Sorin, Milan, Italy). **(B)** Final position of a 23-mm CoreValve EvolutR (Medtronic, Minneapolis, Minnesota) implanted via transfemoral approach. **(C)** Pre-procedural fluoroscopic image of a degenerated 23-mm Sorin Mitroflow. **(D)** Final position of a 23-mm SAPIEN XT (Edwards Lifesciences, Irvine, California) implanted within the SHV through a transfemoral approach. **(E)** Fluoroscopic image of a degenerated 27-mm Carpentier-Edwards Magna (Edwards Lifesciences, Irvine, California). **(F)** Post-procedural fluoroscopic image showing a 29-mm St. Jude Portico (St. Jude Medical Inc, St. Paul, Minnesota) inside the failing SHV. **(G)** Pre-procedural aortogram showing a failing stentless 23-mm Medtronic Freestyle valve with severe aortic regurgitation. **(H)** Post-procedural aortogram showing the final position of the 23 mm SAPIEN XT transcatheter heart valve inside the stentless SHV. Note the absence of aortic regurgitation.

regurgitation) as a mechanism of surgical valve dysfunction were the factors associated with higher transvalvular gradients post-TAVR (Figure 6). In those patients receiving a CoreValve, a depth of implantation >6 mm below the surgical valve was also associated with higher residual gradients.

The mean rate of paravalvular leaks of at least moderate degree following valve-in-valve procedures is 4%, much lower than the ~10% to 12% reported with first-generation transcatheter valves (8). In fact, up to 74% of the patients had none or trace residual leak following a valve-in-valve procedure, which is similar to the results obtained with the last generation of transcatheter valves for treating native aortic stenosis.

There are some major differential aspects between conventional TAVR and valve-in-valve procedures. Table 3 condenses the relative frequencies of the main complications associated with each type of procedure.

LATE OUTCOMES

Only a few valve-in-valve studies have reported 1-year survival rates (10,56,57,59–65). The mean mortality rate at 1 year has been 15.1% (ranging from 0% to 16.8%) (Table 2). Factors associated with increased 1-year mortality were smaller surgical valves, stenosis as a mechanism of valve dysfunction, and use of the transpical approach (Figure 7) (10). No cases of structural valve failure at midterm follow-up were reported in the most important series of valve-in-valve procedures, but further studies with a longer-term follow-up are needed to determine the degeneration rate of transcatheter valves following these procedures.

MITRAL VALVE-IN-VALVE AND VALVE-IN-RING PROCEDURES

Perioperative mortality and morbidity exceeds 15% in patients >75 years of age after reoperation following a first mitral valve intervention (67). Transcatheter valve-in-valve implantation, and, more recently, valve-in-ring procedures have emerged as less invasive alternatives to redo open heart surgery in selected patients deemed at high surgical risk. However, it should be stressed that these new procedures are performed with devices that were initially designed for the aortic or pulmonary valve. Therefore, they are still considered "off-label" and should be performed only as a last resort, when no other feasible options exist.

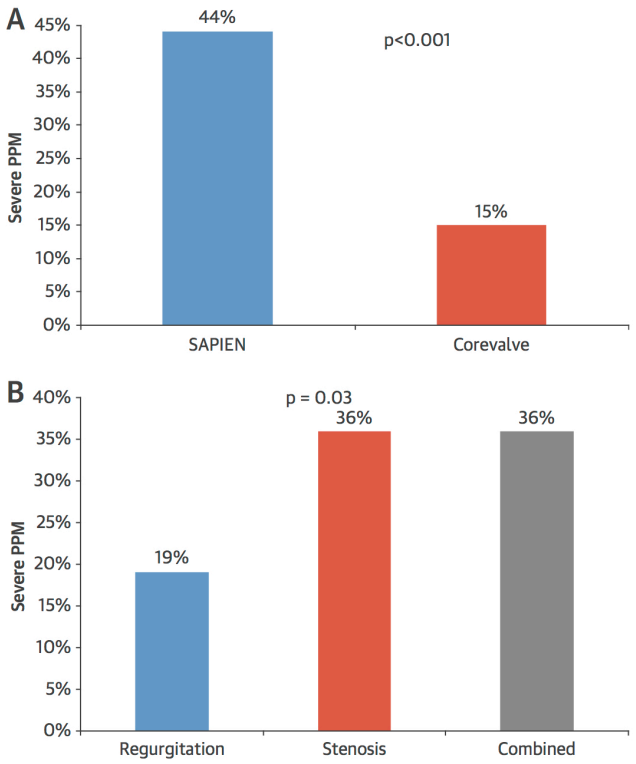
PRE-PROCEDURAL WORK-UP AND PROCEDURAL ASPECTS. Similar to aortic valve-in-valve procedures, an accurate knowledge of the surgical mitral

TABLE 2 Published Case Series (>10 Patients) on Aortic Valve-in-Valve Procedures

First Author, Year (Ref. #)	N	THV	Approach	Age (yrs)	Bioprosthesis Failure AR/AS/Mixed (%)	Logistic EuroSCORE (%)	STS Score (%)	LVEF (%)	Procedural Success (%)	Mean Gradient Post-ViV (mm Hg)	AR > Moderate	Pacemaker	THV Malposition (%)	Coronary Obstruction (%)	PPM (%)	Mortality at 30 days (%)	Mortality at 1 yr (%)
Kempfert et al., 2010 (56)	11	SAPIEN	TA	78	73/0/27	31.7	7.2	53.8	100	11	0	0	NR	NR	NR	0	0
Webb et al., 2010 (36)	10	SAPIEN	TA/TF	82.1	50/10/40	30.4	10	55	100	12.8	0	0	10	NR	NR	0	NR
Pasic et al., 2011 (57)	14	SAPIEN	TA	73.3	NR	45.3	21.9	45	100	13.1	0	0	0	0	NR	0	14.3
Eggebrecht et al., 2011 (58)	47	SAPIEN/ CoreValve	TA/TF	79.8	47/32/21	35	11.6	52	98	17	2	NR	8	NR	NR	17	NR
Bedogni et al., 2011 (59)	25	CoreValve	TF/TAx	82.4	36/64/0	31.5	8.2	56.5	100	13.8	0	12	NR	8	NR	12	16
Bapat et al., 2012 (60)	23	SAPIEN	TA/TF	76.9	61/39/0	31.8	7.6	48	100	9.1	0	0	4.3	0	NR	0	12.5
Seiffert et al., 2012 (61)	11	SAPIEN	TA	79.3	36/36/27	31.8	12.5	50.1	100	17.9	0	NR	NR	NR	45.45	NR	16.6
Latib et al., 2012 (62)	18	SAPIEN	TF/TA/ TAx	75	33/50/17	37.4	8.2	52.9	94	12.4	0	11.7	NR	0	NR	0	5.6
Linke et al., 2012 (63)	27	CoreValve	TF	74.8	22/7/71	31.3	NR	NR	100	18	7.4	3.7	3.7	0	NR	7.4	12
Gaia et al., 2012 (34)	14	Braile Inovare	TA	69.8	NR	42.9	38.6	51	100	12.8	NR	NR	NR	NR	NR	14.3	NR
Dvir et al., 2014 (10)	459	CoreValve/ SAPIEN	TA/TF/ TAO/ TAx	77.6	39/30/30	31.1	9.8	50.3	93.1	15.8	5.4	8.3	15.3	2	31.8	7.6	16.8
Ihlberg et al., 2013 (64)	45	CoreValve/ SAPIEN	TA/TF	80.6	51/29/18	NR	14.6	46.3	95.6	16.4	2	7	2.2	0	NR	4.4	11.9
Subban et al., 2014 (65)	12	SAPIEN/ CoreValve	TF/TS/TA/ TAO	78.5	50/50	NR	7.4	NR	100	15	8.3	16.6	8.3	0	33	0	0
Camboni et al., 2015 (66)	31	SAPIEN/ CoreValve/ others	TA/TF	77.8	22/39/39	NR	20.9	55.6	88	16.1	NR	6	NR	10	NR	22.5	NR

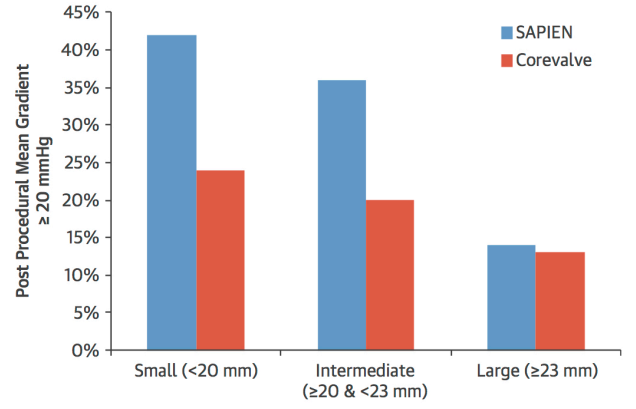
AR = aortic regurgitation; AS = aortic stenosis; LVEF = left ventricular ejection fraction; NR = not reported; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons; TA = transapical; TAO = transaortic; TAx = transaxillary; TF = transfemoral; THV = trancatheter heart valve; TS = transseptal; ViV = valve-in-valve.

FIGURE 5 Incidence of Severe PPM After Valve-in-Valve Procedures



Incidence of severe prosthesis-patient mismatch (PPM) following aortic valve-in-valve procedures, according to valve type **(A)** and the main mechanism of surgical valve failure **(B)** (10).

FIGURE 6 Rate of High Transvalvular Gradients Following Aortic Valve-in-Valve Procedures



Rate of transvalvular gradients ≥20 mm Hg following aortic valve-in-valve procedures, according to surgical bioprosthesis size (10).

prosthesis or ring is essential for planning a mitral valve-in-valve or valve-in-ring procedure. The main characteristics of the SHV have already been outlined in a prior section of this review. Regarding the mitral rings, the D-shape of the annuloplasty ring may result in the occurrence of paravalvular leaks following transcatheter valve implantation. Because ring circularization is important to ensure efficient sealing, a transcatheter valve-in-ring procedure should, perhaps, be limited to deformable complete and rigid semilunar annuloplasty devices. Table 4 summarizes all the known surgical mitral rings amenable to a valve-in-ring procedure. Selection of the most appropriate THV is critical. Indeed, especially during valve-in-ring procedures, the capability of the THV to assume a D-shaped morphology, if needed, (e.g., Direct Flow valve) could become an important asset.

PRE-PROCEDURAL CONSIDERATIONS. Akin to aortic valve procedures, patients should undergo a multidisciplinary team evaluation including cardiologists, cardiothoracic surgeons, anesthesiologists, nurses, and geriatricians. Transthoracic echocardiography and TEE should be performed to assess the severity and mode of bioprosthetic mitral valve failure, as well as left ventricular function. Concomitant coronary disease should be ruled out by a coronary angiogram before the procedure. CT is also very useful to provide information on valve dimensions and other geometric considerations. Left ventricular outflow tract (LVOT) obstruction is one of the potential complications of mitral transcatheter valve procedures, and the proximity between the surgical valve and LVOT, as well as LVOT dimensions should be assessed. However, the exact role of CT measurements in pre-procedural planning needs to be further evaluated (e.g., to better predict the risk of LVOT obstruction).

VALVE SIZING. To optimize anchoring and to limit paravalvular leakage, a minimum of 10% oversizing of the transcatheter valve compared with the true internal diameter of the surgical device is currently recommended (68). It is not appropriate to perform extreme oversizing, as a significantly underexpanded transcatheter valve may lead to incorrect leaflet coaptation, elevated transvalvular gradient, and limited durability.

APPROACH. The majority of mitral valve-in-valve cases are performed within a dedicated hybrid theater or in an operating room under general anesthesia. When the transapical approach is selected, a left mini-thoracotomy is used and purse-string sutures reinforced with pledgets are prepared. The left ventricular apex is punctured, the access sheath is

inserted inside the left ventricle, and a guidewire is advanced under fluoroscopy across the failing bioprosthetic mitral valve into a pulmonary vein. The wire is then exchanged for a stiffer wire. The transcatheter valve (which is crimped in a reverse fashion when an Edwards SAPIEN is used) is then delivered through a standard delivery system. The transcatheter valve is implanted with fluoroscopic and TEE guidance, during rapid ventricular pacing.

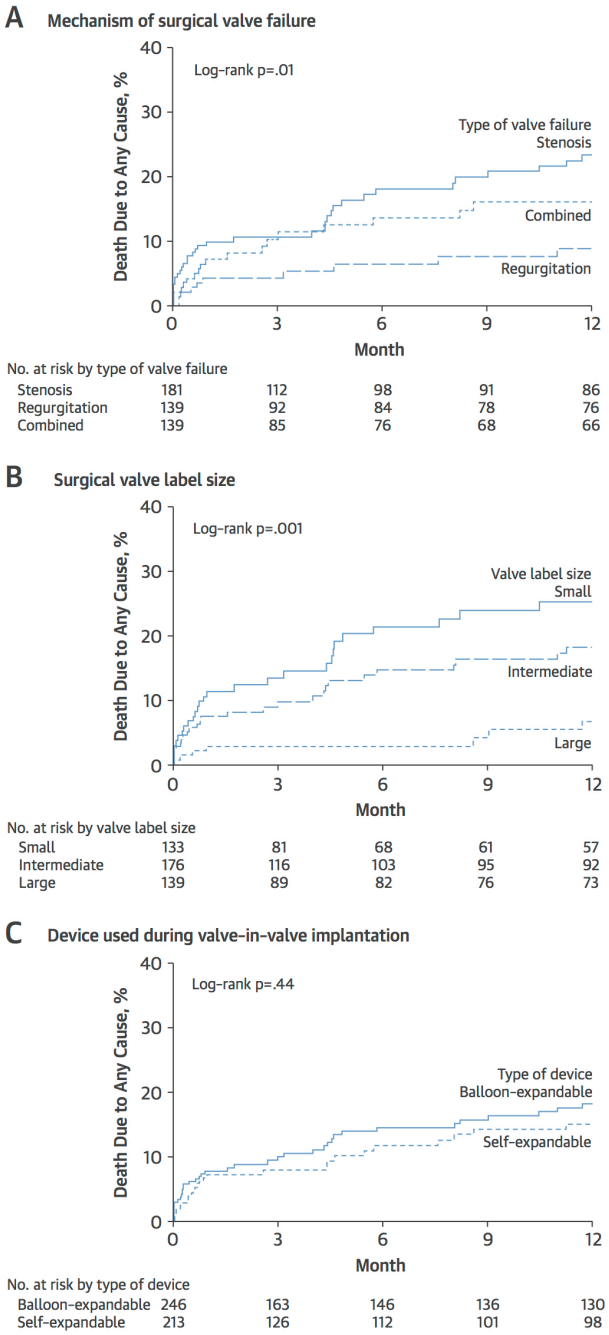
When the transseptal approach is chosen, femoral or jugular venous access is obtained. A transseptal puncture is done in a high and posterior position. After placing a sheath in the left atrium, a bolus of heparin is administered and a guidewire is positioned in the left ventricle. Afterward, a stiffer wire with a J curve at the end is gently placed at the left ventricular apex. Pre-dilation is generally avoided. Then, the valve, mounted for an antegrade implantation, is advanced across the atrial septum and then implanted using a slow balloon inflation technique, under rapid ventricular pacing.

VALVE POSITIONING. The transcatheter valve should be positioned 3 to 5 mm atrially, relative to the sewing cuff of the SHV (69). For mitral valve-in-ring procedures, it is generally recommended to center the transcatheter valve in relation to the ring, with equal portions within the left atrium and the left ventricle (70). Examples of valve-in-valve and valve-in-ring procedures are shown in **Figure 8**.

MITRAL VALVE-IN-VALVE AND VALVE-IN-RING RESULTS

The reported results of the case series of mitral valve-in-valve and valve-in-ring published to date (43,44,68,70-76) are shown in **Table 5**. A total of 113 patients (77 valve-in-valve, 36 valve-in-ring) have been reported, with a mean age of 72 years, and a very high surgical risk profile (mean logistic Euroscore and STS scores of 40% and 13.8%, respectively). Most procedures (64%) were performed via a transapical approach and 36% of cases were performed via a transseptal approach. The Edwards SAPIEN XT valve was used in most cases (83%), and the Melody valve was used in 12% of patients. The transcatheter valve was successfully implanted in 94.5% of cases, and mean 30-day mortality rate was 8.2% (**Central Illustration**). LVOT obstruction occurred in 8.3% of patients undergoing valve-in-ring implantation (n = 3), with no reported cases in valve-in-valve procedures. Mean transvalvular gradient post-valve implantation was 6.3 mm Hg and

FIGURE 7 Mortality Rates at 1-Year Follow-Up After Aortic Valve-in-Valve Procedures



Mortality rates following aortic valve-in-valve procedures, according to the main mechanism of surgical valve dysfunction **(A)**, surgical valve size **(B)**, and type of transcatheter valve **(C)**. Reprinted with permission from Dvir et al. (10).

TABLE 3 Main Complications Associated With Aortic Valve-in-Valve Procedures and Conventional TAVR

Complications	Valve-in-Valve	Conventional TAVR
Elevated post-procedural gradients	+++	+
Coronary obstruction	+++	+
Malpositioning	++	+
Vascular complications	++	++
Permanent pacemaker	+	++
Paravalvular leak	–	++
Annulus rupture	–	+

TAVR = transcatheter aortic valve replacement.

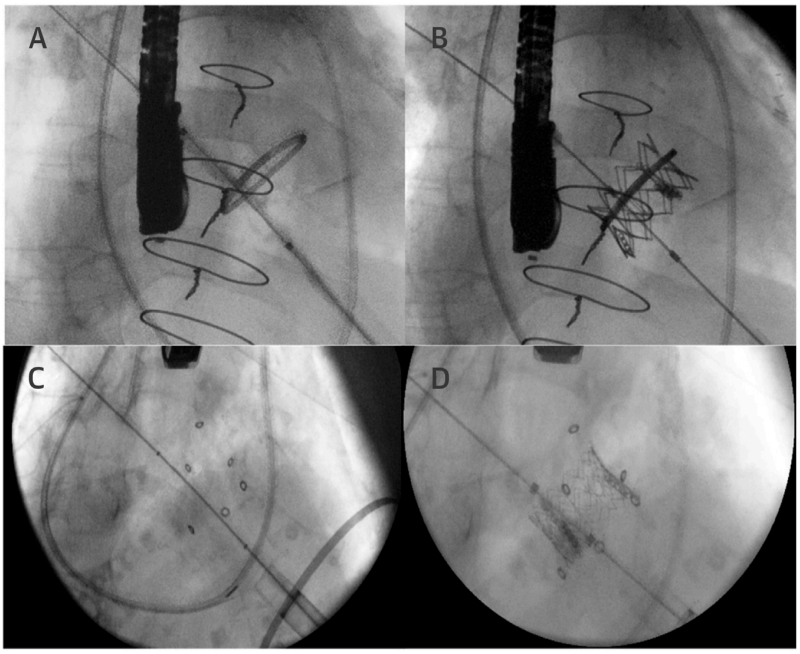
TABLE 4 Surgical Mitral Rings Within Which Transcatheter Heart Valves Have Been Implanted

Complete rings and band
Edwards Physio I/II
Medtronic Duran
St. Jude Seguin
Sorin Carbomedics
Medtronic Profile 3D
Incomplete rings and bands
Edwards Classic
Cosgrove-Edwards Band

residual leaks of at least moderate degree were observed in 3.5% of patients.

The results of a retrospective collection of data from multiple centers worldwide were recently presented (45). This study included a total of 349 and 88 patients who underwent a mitral valve-in-valve and valve-in-ring procedure, respectively. The access route was transapical (78.9%), transseptal after jugular or femoral venous access (18.5%), and direct left atrium (2.5%). The mean age of the study population was 74 years, with 60% women, and a mean STS score of 12.9%. The mechanisms of failure were regurgitation, stenosis, and combined mode in 45%, 23%, and 32% of patients, respectively. The vast majority of the mitral procedures were done under general anesthesia (98.9%) and a balloon pre-dilation was performed in only 24% of cases. Malpositioning of the transcatheter valve occurred in 6.6% of cases

FIGURE 8 Examples of Mitral Valve-in-Valve and Valve-in-Ring Procedures



(A) Fluoroscopic image of a 28-mm Edwards Physio 1 ring (Edwards Lifesciences, Irvine, California). **(B)** Final fluoroscopic image after the implantation of a 23-mm Edwards Sapien XT transcatheter heart valve inside the ring (valve-in-ring procedure) via a transapical approach. **(C)** Fluoroscopic image of a failing 23-mm Mosaic valve (Medtronic, Minneapolis, Minnesota) in the mitral position. **(D)** Post-procedural fluoroscopic image showing a 23-mm Edwards Sapien XT transcatheter heart valve implanted within the SHV through a transapical route.

and LVOT obstruction in 6.9% of cases (2.6% and 8% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.03). At 30 days, the rate of all-cause death was 8.5% (7.7% and 11.4% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.15) and the occurrence of stroke was 2.5% (2.9% and 1.1% in valve-in-valve and valve-in-ring procedures, respectively; p = 0.33). The main procedural results according to the type of procedure (valve-in-valve vs. valve-in-ring) are summarized in **Figure 9**.

Predictors of suboptimal valve hemodynamic results were also evaluated. The main predictor of post-procedural elevated mitral gradients (≥10 mm Hg) was the presence of a small surgical valve size (label size ≤25 mm). Significant residual mitral regurgitation (≥moderate) was more frequent after mitral valve-in-ring than after valve-in-valve procedures (14.8% vs. 2.6%; p < 0.001) (**Figure 9**).

The late results (>3 months) of valve-in-valve and valve-in-ring procedures are limited to 7 reports, including a total of 93 patients (43,68,70,71,73,75,76). The mortality rate after a mean follow-up of 14 months was 20.5%. Four cases of valve thrombosis were reported, all >30 days after a valve-in-valve procedure (70,74). During follow-up, 1 patient underwent a second transapical valve-in-valve implantation due to transcatheter valve migration 2 months after an uneventful valve-in-valve procedure (68). There were no cases of late structural valve failure requiring reintervention.

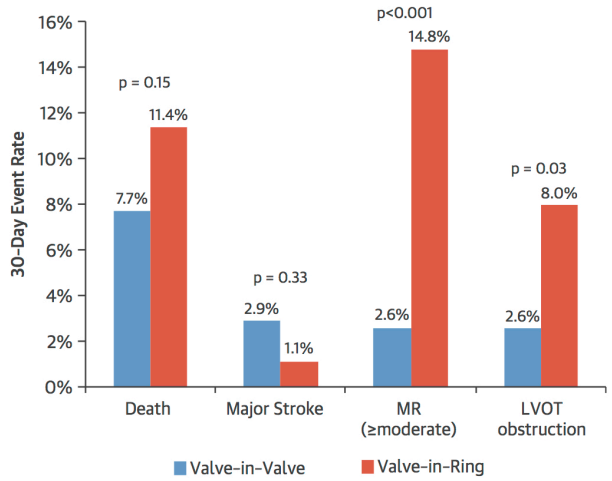
In summary, the preliminary experience with mitral valve-in-valve and valve-in-ring procedures has outlined its feasibility, with acceptable clinical and hemodynamic 30-day and late results, despite the high-risk profile of the treated population. Most procedures were performed via a transapical approach, which is more invasive, yet more direct, and an easier approach for such procedures. However, a progressive shift towards a higher use of the transfemoral/transseptal approach is likely to be seen in the coming years. Of note, valve-in-ring procedures were associated with a much higher risk of major complications, including a higher rate of residual regurgitation and LVOT obstruction. A better understanding of the ring characteristics leading to these greater failure rates is required. Preliminary data suggests that subacute or late valve thrombosis rates may be more frequent in transcatheter valves positioned within the mitral (vs. aortic) position, further outlining that anticoagulation therapy following these procedures may be the preferred antithrombotic strategy. Finally, close clinical follow-up of these patients will be required to determine valve durability and potential late complications.

TABLE 5 Published Case Series on Mitral Valve-in-Valve and Valve-in-Ring Procedures

First Author, Year (Ref. #)	N	THV	Approach	Age (yrs)	Logistic EuroScore (%)	STS Score (%)	LVEF (%)	Procedural Success (%)	Valve Embolization (%)	Mean Gradient Post (mm Hg)	Moderate or Severe Residual MR (%)	Stroke	Short-Term Mortality (30 Days/ In-Hospital) (%)	Valve Thrombosis (%)	Late Mortality (%)	Follow-Up (months)
Mitral Valve-in-Valve																
Cerillo et al., 2011 (71)	3	SAPIEN	TA	67.7	59.9	15.2	36.6	NR	33.3	5	0	0	33	0	33	7.4
Seiffert et al., 2012 (72)	6	SAPIEN	TA	74.3	33	19	55.8	100	0	5.5	0	0	16.7	NR	NR	NR
Cullen et al., 2013 (43)	9	Melody	TS	74.8	NR	13.3	55	100	0	5.2	11.1	0	22.2	0	33.3	3.7
Cheung et al., 2013 (68)	23	SAPIEN	TA	81	NR	12.6	54.5	100	0	6.9	0	4.4	0	0	9.6	25.1
Schäfer et al., 2014 (73)	8	SAPIEN	TA-TS	69.1	36.2	10.8	NR	100	0	5.3	0	12.5	0	0	0	6
Wilbring et al., 2014 (70)	10	SAPIEN	TA	75	54.7	11.6	NR	100	0	6.2	0	0	10	20	10	3
Whisenant et al., 2015 (74)	7	SAPIEN	5 TA 2 TF	NR	NR	NR	NR	100	0	<5	0	0	NR	28.6	NR	NR
Kliger et al., 2015 (44)	5	Melody	TS-TA	72.6	25.9	15.1	54	80	20	5	0	0	0	NR	NR	NR
Bouleti et al., 2015 (75)	6	SAPIEN	TF-TS	61	37	18	55.3	66.6	16.6	8	0	0	16.7	0	33.3	22.4
Mitral Valve-in-Ring																
Descoutures et al., 2013 (76)	17	SAPIEN	8 TS 9 TA	70	36	13	22	88	0	7	11.8	0	18	0	29	13
Schäfer et al., 2014 (73)	4	SAPIEN	TA	69	45.1	8.7	NR	100	0	5.3	0	0	0	0	50	6
Wilbring et al., 2014 (70)	2	SAPIEN	TA	75	54.7	11.6	NR	100	0	6	0	0	50	0	50	3
Whisenant et al., 2015 (74)	2	SAPIEN	TA	NR	NR	NR	55.3	100	0	<5	0	0	NR	0	NR	NR
Bouleti et al., 2015 (75)	11	SAPIEN	TF-TS	61	37	18	22	90.9	0	8	9	0	0	0	18.2	22.4

MR = mitral regurgitation; NR = not reported; other abbreviations as in Table 2.

FIGURE 9 30-Day Outcomes After Mitral Valve-in-Valve and Mitral Valve-in-Ring Procedures



Thirty-day rates of death, major stroke, mitral regurgitation ≥ moderate (MR), and left ventricular outflow tract (LVOT) obstruction following transcatheter mitral valve-in-valve (n = 349) and valve-in-ring (n = 88) procedures (45).

VALVE-IN-VALVE PROCEDURES: UNRESOLVED ISSUES AND FUTURE DIRECTIONS

The valve-in-valve proof-of-concept described by Walther et al. (9) in 2007 heralded a new era of transcatheter-based heart valve therapies. Since then, due to its less invasive and appealing nature to both patients and physicians alike, when compared with redo open-heart surgery, valve-in-valve procedure rates continue to grow rapidly. Nonetheless, aortic valve-in-valve procedures still include several safety concerns, such as a higher rate of valve malpositioning (especially in cases of stentless valves, with aortic regurgitation as the main mechanism of failure), coronary obstruction, and elevated transvalvular gradients (particularly in smaller surgical valves). The arrival of newer-generation transcatheter valves with repositionability and retrievability properties should reduce the incidence of some of these complications. Also, nonrandomized data suggest a valve-type effect influencing the hemodynamic results of valve-in-valve procedures, with a supra-annular valve leaflet position within the transcatheter valve stent frame serving as an important factor determining improved hemodynamics (i.e., lower residual transvalvular gradients). One could therefore postulate that the optimal design for future transcatheter devices for valve-in-valve procedures should contain: 1) a thin stent frame structure, probably without any bulky additional antiparavalvular leak features that could increase transvalvular gradients post-procedure; 2) repositionability and retrievability properties; 3) a mechanism for grasping the surgical valve leaflets in order to avoid coronary obstruction; and 4) a supra-annular position of the valve leaflets within the stent frame, in order to improve valve hemodynamics.

Whereas data on long-term (up to 5 years) THV durability following standard (for native valves) TAVR procedures is promising (77), there are scarce data on long-term durability of transcatheter valves following valve-in-valve procedures (68,78). However, it appears conceivable to anticipate a reduction in valve durability in the setting of valve-in-valve procedures, especially in cases of elevated gradients and when underexpansion is substantial (79).

For mitral valve-in-valve and valve-in-ring procedures, the risk of LVOT obstruction, valve thrombosis, and unknown durability are some of the unresolved issues linked with such procedures. In addition, both the best antithrombotic regime and the specific anatomic and patient characteristics increasing the risk of a mitral transcatheter procedure are yet to be determined.

Although we recognize the current limitations of valve-in-valve procedures, the growth of this technology in the near future is inevitable. It is therefore conceivable that the selection of valve type and technique during SAVR could be influenced by the convenience of a transcatheter valve-in-valve technique at a later time period. In younger individuals undergoing SAVR, the future availability of less invasive procedural options to treat structural valve failure could become an argument in favor of implanting a surgical tissue valve. Moreover, during the index surgical procedure, the benefits of annular enlargement or other techniques to obtain the largest effective orifice area possible may be considered in order to avoid PPM post-surgery. This will also enable enhanced optimization of potential future valve-in-valve procedures, should the surgical valve ultimately fail. Also, aortic SHVs which carry an increased risk for coronary obstruction post-transcatheter valve-in-valve therapy may be implanted less frequently, considering the risk of future bioprosthetic valve failure and the potential requirement for a valve-in-valve procedure. Bearing in mind preliminary data suggesting the lower mortality rate after valve-in-valve procedures when the major mode of failure of tissue valves is regurgitation, the treatment paradigm shift in SAVR may also

include a greater implantation rate of SHVs with regurgitation as the predicted main mechanism of degeneration.

Even if current data supports the use of valve-in-valve procedures for most patients, a thorough multidisciplinary heart team approach is strongly recommended for every patient considered for this type of transcatheter therapy. Long-term follow-up and increasing the worldwide clinical experience will be fundamental for establishing the exact role of valve-in-valve implantation for treating degenerative bioprosthetic valves, as well as for addressing the numerous knowledge gaps associated with these innovative procedures.

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KEY WORDS **bioprosthetic dysfunction, transcatheter aortic valve replacement, valve failure**

Artículo IV: "Incidence, Causes, and Predictors of Early (≤30 Days) and Late Unplanned Hospital Readmissions After Transcatheter Aortic Valve Replacement."

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Incidence, Causes, and Predictors of Early (≤30 Days) and Late Unplanned Hospital Readmissions After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The aim of this study was to determine the incidence, causes, and predictors of unplanned hospital readmissions after transcatheter aortic valve replacement (TAVR).

BACKGROUND Data regarding unplanned hospital readmissions after TAVR in a real-world all-comers population are scarce.

METHODS A total of 720 consecutive patients undergoing TAVR at 2 centers who survived the procedure, were included. Median follow-up was 23 months (interquartile range [IQR]: 12 to 39 months), available in 99.9% of the initial population. The occurrence, timing, and causes of hospital readmission within the first year post-TAVR were obtained in all cases. Early and late readmissions were defined as those occurring ≤30 days and >30 days to 1 year post-TAVR, respectively.

RESULTS There were 506 unplanned readmissions in 316 patients (43.9%) within the first year post-TAVR (median time: 63 days; IQR: 19 to 158 days post-discharge). Of these, early readmission occurred in 105 patients (14.6%), and 118 patients (16.4%) had multiple (≥2) readmissions. Readmissions were due to noncardiac and cardiac causes in 59% and 41% of cases, respectively. Noncardiac readmissions included, in order of decreasing frequency, respiratory, infection, and bleeding events as the main causes, whereas heart failure and arrhythmias accounted for most cardiac readmissions. The predictors of early readmission were periprocedural major bleeding complications ($p = 0.001$), anemia ($p = 0.019$), lower left ventricular ejection fraction ($p = 0.042$), and the combined presence of antiplatelet and anticoagulation therapy at hospital discharge ($p = 0.014$). The predictors of late readmission were chronic obstructive pulmonary disease ($p = 0.001$), peripheral vascular disease ($p = 0.023$), chronic renal failure ($p = 0.013$), and atrial fibrillation ($p = 0.012$). Early readmission was an independent predictor of mortality during the follow-up period (hazard ratio: 1.56, 95% confidence interval: 1.02 to 2.39, $p = 0.043$).

CONCLUSIONS The readmission burden after TAVR in an all-comers population was high. Nearly one-fifth of the patients were readmitted early after hospital discharge, increasing the risk of mortality at follow-up. Reasons for readmission were split between noncardiac and cardiac causes, with respiratory causes and heart failure as the main diagnoses in each group, respectively. Whereas early readmissions were mainly related to periprocedural bleeding events, most late readmissions were secondary to baseline patient comorbidities. These results underscore the importance of and provide the basis for implementing specific preventive measures to reduce readmission rates after TAVR. (J Am Coll Cardiol Intv 2015;8:1748–57) © 2015 by the American College of Cardiology Foundation.

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Unplanned readmissions after initial hospitalization are frequent, significantly affecting clinical outcomes, patient quality of life, and health care costs (1,2). Early (within 30 days of discharge) readmissions have generated significant debate. As many as 20% of Medicare beneficiaries are readmitted within 30 days after an index hospitalization, and this has been associated with additional health care costs exceeding $15 billion (1). Of note, the rate of early unplanned readmissions has been considered a marker of quality of care and hospital performance (3,4), and the subject of provider payment restrictions in the United States. Identifying the timing, causes, and predictors of unplanned readmissions is thus fundamental for implementing appropriate preventive measures.

Transcatheter aortic valve replacement (TAVR) is currently the standard treatment for severe aortic stenosis in symptomatic patients with prohibitive or high surgical risk (5). The significant burden of comorbidities in patients currently undergoing TAVR, as well as the relatively high rate of periprocedural complications, engenders a high likelihood of hospital readmissions in such patients. However, data on unplanned readmissions after TAVR are scarce, particularly regarding the timing, specific causes, and predictors of readmission. More importantly, no data exist on 30-day readmissions after TAVR apart from reporting its incidence (6–8). The objectives of this study were to determine the incidence, causes, and predictive factors of unplanned hospital readmissions after TAVR, with a specific focus on readmissions within the 30-day and 1-year periods.

METHODS

STUDY POPULATION. A total of 893 consecutive patients with symptomatic severe aortic stenosis who underwent TAVR at 2 centers were evaluated for the study. Of these, patients who died before hospital discharge (n = 65) or those with follow-up of less than 1 year (n = 108) were excluded, leading to a final population of 720 patients. The indications for TAVR and procedural approach were assessed by each center's heart team composed of interventional cardiologists and cardiac surgeons. The TAVR procedures were performed using balloon- and self-expanding valves, as previously described (5). In-hospital and follow-up data were prospectively entered in a dedicated database. Clinical outcomes were defined according to Valve Academic Research Consortium-2 criteria (9). All patients signed informed consent forms before the procedure, and all studies were performed in accordance with the local ethics committee of each center.

FOLLOW-UP. Clinical follow-up was carried out during pre-scheduled outpatient clinic visits or by telephone contact at 1, 6, and 12 months post-TAVR and yearly thereafter. Records from referring cardiologists, general practitioners, and other hospitals were consulted whenever necessary for further information. Complete information about readmissions within the last follow-up was obtained in 99.9% of patients (1 patient was lost to follow-up). The median length of follow-up of the study population was 23 months (interquartile range [IQR]: 12 to 39 months).

HOSPITAL READMISSION. Readmissions were defined as a patient being admitted to a hospital ward or an intensive care unit. Visits to the emergency department or admission to a day-stay hospital were excluded from the current analysis. Readmission date, duration of hospital stay, primary and secondary reasons for hospitalization, and in-hospital death were recorded after a detailed medical records review. The primary diagnosis on the discharge report was used to determine the main cause of readmission. Causes of readmission were grouped as being of cardiac or noncardiac origin. Cardiac causes included the following: heart failure, acute coronary syndrome (unstable angina or myocardial infarction), arrhythmia, and prosthesis related (endocarditis, valve thrombosis, structural failure of the valve requiring intervention). Noncardiac causes were classified as follows: respiratory (including pneumonia), bleeding, cerebrovascular event (ischemic or hemorrhagic stroke, transient ischemic attack), peripheral vascular events, infections, trauma, and other.

Time to readmission was calculated as the time between the date of hospital discharge after the index TAVR procedure (time 0) and the first hospital readmission day. Readmissions were also classified according to the timing as early (≤30 days) or late (between 30 days and 12 months). Multiple readmissions were defined as ≥2 readmissions.

STATISTICAL ANALYSIS. Categorical variables were expressed as number (percentage) and continuous variables as mean ± SD or median (IQR: 25th to 75th percentiles) according to their distribution. Assessment of normality for continuous data was performed using the Shapiro-Wilks test. Comparison of numerical variables was performed with the 2-sided Student *t* test or Wilcoxon rank sum test, and the chi-square

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HR = hazard ratio
IQR = interquartile range
TAVR = transcatheter aortic valve replacement

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or Fisher exact test was used to compare qualitative variables. We determined unadjusted all-cause early, late, and overall readmission rates. Analysis of the predictors of hospital readmissions was performed using the conditional Prentice-Williams-Peterson model (10) to account for multiple events. Variables with a p value <0.05 on univariate analysis were entered into a logistic regression analysis to determine the independent predictors of early, late, and overall readmissions. Univariate and multivariate competing-risk (mortality not occurring during a hospital admission) regression analyses were done to determine the predictors of readmissions. Freedom from readmission and mortality curves were calculated with the Kaplan-Meier method, and comparison between groups was performed with the log-rank test. A landmark analysis excluding patients who died at <30 days was used to further investigate the impact of early readmission on 2-year mortality. A p value <0.05 was considered significant for all statistical tests. All data were analyzed with the Statistical Package for Social Sciences version 20.0 (SPSS Inc., IBM, Armonk, New York) and the R statistical software, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The main baseline, procedural characteristics, and in-hospital complications of the study population are shown in Table 1.

INCIDENCE, TIMING, AND CAUSES OF HOSPITAL READMISSIONS. A total of 316 patients (43.9%) were readmitted during the first year after the index TAVR procedure, with a total of 506 readmission episodes (70.4% total readmissions per index discharge and 1.6 episodes per admitted patient). A total of 198 patients (27.5%) experienced 1 readmission, and 118 patients (16.4%) had multiple (≥2) readmissions, ranging from 2 to 7. The median time from the TAVR procedure discharge to the first readmission was 63 days (IQR: 19 to 157 days). The median length of stay per readmission was 7 (IQR: 4 to 13 days).

The timing of hospital readmission within the year after TAVR is shown in Figure 1. Early (≤30 days) readmission occurred in 105 patients (14.6%) with 115 readmission episodes (10 patients had 2 readmissions). This represented 33.2% of total readmitted patients within the year after TAVR. As many as 41 patients (5.7%) were readmitted within the 7 days after TAVR. A total of 88 patients were readmitted between 30 days and 3 months, leading to a readmission rate of 26.8% within the 3 months after TAVR. An additional 123 patients (17.1%) required hospital readmission between 3 and 12 months after TAVR.

The causes of readmission within the first year are summarized overall and according to timing in Table 2. Of 506 readmission episodes, 298 (58.9%) were due to noncardiac causes, mostly respiratory (20.1%), infection (15.4%), and bleeding (12.1%) events. Cardiac origin accounted for 208 readmission episodes (41.1%), mainly due to heart failure (56.7%) and arrhythmic events (21.2%). Bradyarrhythmias accounted for 18 events, and tachyarrhythmias accounted for 28 events (17 atrial arrhythmias and 9 ventricular arrhythmias). One-fourth of readmissions due to cardiac reasons required an invasive procedure.

Early readmissions were also predominantly noncardiac in origin (57.4%), secondary to infections (18.2%, mainly access-site infections) and respiratory (16.7%) or bleeding (15.1%) events. Cardiac causes accounted for 42.6% of early readmissions, with the vast majority of patients being readmitted because of heart failure (71.4%). There were no differences between the main causes (cardiac vs. noncardiac) of early and late readmission after TAVR (p = 0.71). However, from the perspective of cardiac etiology-driven readmissions, heart failure was more frequently a cause of early instead of late readmission (p = 0.018).

The Kaplan-Meier curves of readmission events (patient based) over time overall and according to the underlying causes (cardiac vs. non-cardiac) are shown in Figure 2.

PREDICTORS OF HOSPITAL READMISSION. The predictors of early and late hospital readmission after TAVR are shown in Tables 3 and 4, respectively. The independent predictors of early readmissions were procedural complications deemed major or life-threatening bleeding (hazard ratio [HR]: 2.41, 95% confidence interval [CI]: 1.57 to 3.70; p = 0.001), left ventricular ejection fraction (HR: 1.08 for each decrease of 5%, 95% CI: 1.00 to 1.17; p = 0.042), hemoglobin levels (HR: 1.19 for each decrease of 1 g/dl, 95% CI: 1.03 to 1.39; p = 0.019), and combination antithrombotic therapy (anticoagulation + antiplatelet) (HR: 1.62, 95% CI: 1.10 to 2.39; p = 0.014) at hospital discharge. The independent predictors of late readmissions were chronic obstructive pulmonary disease (HR: 1.49, 95% CI: 1.21 to 1.84; p = 0.001), atrial fibrillation (HR: 1.32, 95% CI: 1.06 to 1.63; p = 0.012), peripheral vascular disease (HR: 1.29, 95% CI: 1.04 to 1.61; p = 0.023), and renal function at hospital discharge (HR: 1.05 for each eGFR decrease of 10 ml/min, 95% CI: 1.01 to 1.09; p = 0.013). The factors independently associated with multiple (≥2 vs. 1)

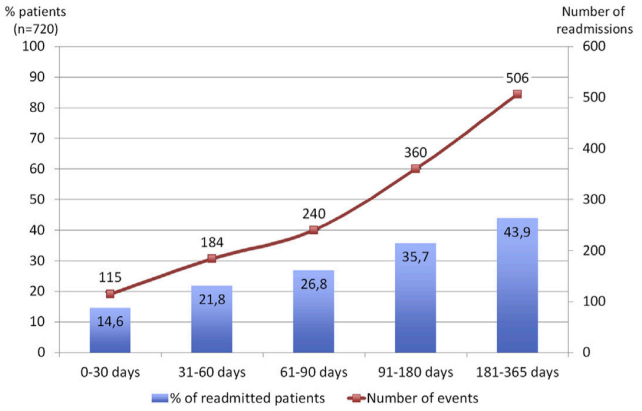
TABLE 1 Baseline Clinical and Procedural Characteristics and In-Hospital Outcomes of the Study Population (N = 720)

Baseline variables	
Age, yrs	82 (77-86)
Male	301 (41.8)
Body mass index, kg/m^2	27.3 ± 5.3
NYHA functional class	
I–II	186 (25.8)
III–IV	534 (74.1)
Diabetes	241 (33.5)
Hypertension	614 (85.3)
Coronary artery disease	412 (57.2)
Previous CABG	194 (26.9)
Atrial fibrillation (chronic/paroxysmal)	239 (33.2)
Previous pacemaker	88 (12.2)
Previous stroke	112 (15.6)
Peripheral vascular disease	178 (24.7)
COPD	179 (24.9)
eGFR <60 ml/min	364 (50.6)
Logistic EuroSCORE	16.6 (10.1-25-0)
Echocardiographic variables	
LVEF, %	55.1 ± 14.6
Mean aortic gradient, mm Hg	43.0 ± 16.4
Aortic valve area, cm^2	0.60 (0.50-0.77)
Procedural characteristics	
Approach	
Transfemoral	481 (66.5)
Not transfemoral	239 (33.2)
Prosthesis type	
Balloon-expandable	609 (84.6)
Self-expandable	111 (15.4)
Prosthesis size, mm	
≤23	301 (41.8)
24-28	281 (39.0)
≥29	133 (18.5)
In-hospital complications	
Need for a second valve	25 (3.5)
Conversion to open heart surgery	16 (2.2)
New permanent pacemaker	76 (10.6)
New persistent left bundle branch block	95 (13.2)
Stroke	17 (2.4)
Major vascular complication	60 (8.3)
Major or life-threatening bleeding	98 (13.6)
Acute kidney injury	144 (20.0)
Echocardiographic variables at hospital discharge	
LVEF, %	55.6 ± 13.0
Mean aortic gradient, mm Hg	10.6 ± 6.1
Aortic regurgitation (moderate-severe)	54 (7.5)
Mitral regurgitation (grades 3-4)	70 (9.7)
Treatment at hospital discharge	
None	12 (1.7)
Single antiplatelet therapy	95 (13.2)
Dual antiplatelet therapy	338 (46.9)
Single anticoagulation therapy	50 (6.9)
Antiplatelet + anticoagulation therapy	202 (28.1)
Hospitalization length, days	7 (5-9)

Values are median (interquartile range), n (%), or mean ± SD.

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

FIGURE 1 Percentage of Unplanned Hospital Readmissions After TAVR



The percentage of readmitted patients and number of readmission episodes within the year after TAVR, grouped according to the timing of readmission. TAVR = transcatheter aortic valve replacement.

readmissions within 1 year were lower mean gradient at baseline (HR: 1.08, 95% CI: 1.02 to 1.15; p = 0.011) and major or life-threatening bleeding (HR: 2.36, 95% CI: 1.50 to 3.71; p = 0.001).

READMISSIONS AND MORTALITY. A total of 44 patients (13.9%) died during a readmission episode (25 of them [7.9%] during the first readmission episode).

In a sensitivity analysis, we evaluated the impact of 30-day readmissions on 30-day to 2-year mortality. The mortality rate at 2-year follow-up was 20.8% (95% CI: 17.5% to 24.1%). In those patients readmitted within 30 days after TAVR, the mortality rate at 2 years was 30.2% (95% CI: 20.4% to 40.0%) compared with 19.2% (95% CI: 15.7% to 22.7%) in those without 30-day readmission (log-rank p = 0.002) (Figure 3). Early readmission was a factor associated with a higher mortality rate (30-day to 2-year) (HR: 1.89, 95% CI: 1.25 to 2.87; p = 0.003), and this association persisted after adjusting for confounding factors in a multivariable analysis (Table 5).

DISCUSSION

Almost one-half of the patients undergoing TAVR were readmitted within the first year after the procedure, and about one-fourth of such readmissions occurred within the first 30 days post-TAVR (30-day readmission rate, ~15%). Multiple readmissions were observed in more than one-third of such patients. Most (~60%) readmissions were due to noncardiac causes, with respiratory failure, infection,

TABLE 2 Causes of Hospital Readmission Within the Year After TAVR, Overall and According to the Timing of Readmission

Causes of Readmission	Overall, 1 Year (n = 506)	Early, ≤30 Days (n = 115)	Late, 30-365 Days (n = 391)
Cardiac causes	208 (41.1)	49 (42.6)	159 (40.7)
Heart failure	118 (23.3)	35 (30.4)	83 (21.2)
Arrhythmia	44 (8.7)	11 (9.6)	33 (8.4)
Bradyarrhythmia	18	2	16
Ventricular arrhythmia	9	3	6
Rapid atrial/flutter fibrillation	17	6	11
Acute coronary syndrome	27 (5.3)	2 (1.7)	25 (6.4)
Myocardial infarction	17	1	16
Unstable angina	10	1	9
Prosthesis related	19 (3.7)	1 (0.9)	18 (4.6)
Endocarditis	12	1	11
Valve thrombosis	2	0	2
Total events requiring an invasive cardiac procedure	50 (9.9)	7 (6.1)	43 (11.0)
Pacemaker implantation	18	3	15
Cardioverter defibrillator implantation	5	1	4
Repeat coronary angiography or PCI	14	1	13
Prosthesis intervention (surgery/percutaneous)	5	0	5
Arrhythmia ablation	4	1	3
Upgrade to cardiac resynchronization therapy	1	0	1
Thoracocentesis	1	0	1
Mitral valve surgery	1	0	1

Continued on the next page

and bleeding events accounting for more than one-half of such events. Approximately 40% of readmissions were secondary to cardiac causes, with heart failure accounting for more than one-half of such cases. Readmissions requiring prosthetic valve reintervention were infrequent. Although periprocedural bleeding complications, anemia, lower left ventricular ejection fraction, and more intensive antithrombotic treatment regimen on hospital discharge were the main predictors of 30-day readmissions, baseline comorbidities such as chronic obstructive pulmonary disease, renal failure, peripheral vascular disease, and atrial fibrillation identified a group of patients with a higher likelihood of delayed readmission. Patients requiring early rehospitalization had a higher mortality risk during the follow-up period.

Several studies have evaluated 30-day readmission rates after cardiac interventions. These ranged from 9% to 24% after percutaneous coronary interventions and cardiac surgery (11–16). In patients undergoing isolated aortic valve replacement, the 30-day readmission rates were ~20% (16), marginally higher than the 15% rate observed in our study. According to our findings, Holmes et al. (6) reported a 30-day readmission rate of 17% in a large series of real-world consecutive patients who underwent TAVR in the TVT (Transcatheter Valve Therapies) registry. At 1-year follow-up, the readmission rate increased to nearly 50%, similar to the 44% reported in the present analysis. In addition, we report for the first time that as many as one-third of patients requiring hospital readmission post-TAVR are in fact hospitalized on multiple occasions (mean, 2.6 ± 1.0) within the year after TAVR. This represents a significant readmission burden, much higher than those observed in previous studies involving cardiac interventions (17) and close to those observed after heart failure hospitalizations (18,19). The additional costs associated with such a high rehospitalization rate may lead some to question the cost-effectiveness of TAVR in an all-comers setting. These data suggest the need to better define risk factors associated with post-TAVR readmissions to implement appropriate preventive strategies.

CAUSES OF HOSPITAL READMISSION POST-TAVR. The reasons for repeat hospitalization after TAVR were diverse and included a broad of range of cardiac and noncardiac etiologies. Noncardiac causes represented the main reason for hospital readmissions in ~60% of patients, and respiratory, infection, and bleeding-related events accounted for approximately one-half of such readmissions. These rates mimic those reported for mortality causes in TAVR patients (20–23) and highlight the importance of comorbid conditions in this population. Pneumonia has been described as the most frequent cause of noncardiac readmission after hospital discharge (1) and was also the most common noncardiac cause for hospital readmission in the present analysis. Other infections, predominantly access site and genitourinary, were also frequent. Special attention to proven strategies for reducing respiratory and access-site infections may be critical to improve readmission rates (24,25). Furthermore, bleeding (mostly gastrointestinal) and vascular events were important factors related to hospital readmission. It has been shown that major late bleeding events are a strong predictor of late mortality after TAVR and increase the risk of rehospitalization (26). This underscores the difficulties in selecting the most appropriate antithrombotic treatment in this elderly and high-risk population, emphasizing the cautionary use of overly aggressive antithrombotic regimens (27). Finally, although readmissions due to traumatic causes were relatively infrequent, post-discharge rehabilitation programs to improve physical fitness and avoid falls and fractures in this frail population may be of the utmost importance as a preventive strategy as well as for improving patients' quality of life.

Approximately 40% of unplanned hospital readmissions after TAVR were due to cardiac causes, and heart failure accounted for more than one-half of such rehospitalizations. Importantly, a significant proportion of such readmissions occurred within the 30 days after hospital discharge. Although only one-fifth of patients undergoing TAVR have a reduced left ventricular ejection fraction, heart failure remains the most important single cause of mortality and rehospitalization among TAVR patients (22,28). A higher left ventricular mass regression post-TAVR has been reported as an independent factor of late rehospitalizations due to heart failure (8). This suggests an important role for diastolic dysfunction in such patients and underscores the importance of intervening before excessive ventricular hypertrophy and advanced fibrosis occurs. It has been shown that the vast majority of patients undergoing TAVR have elevated N-terminal pro-B-type natriuretic peptide levels irrespective of ventricular function parameters (29). Also, the high prevalence of comorbidities such as hypertension, anemia, renal dysfunction, atrial fibrillation, and concomitant significant mitral regurgitation may also contribute to the high rate of heart failure rehospitalization after TAVR. Although we did not find an association between significant post-TAVR aortic regurgitation, this factor has been reported to increase N-terminal pro-B-type natriuretic peptide levels and rehospitalization due to heart failure in previous studies (8,30). This highlights the critical role of implementing post-TAVR programs with closer follow-up similar to those used for heart failure patients to reduce the rehospitalization burden (31,32). Meanwhile, the involvement of the already well-established heart failure clinics may represent a very first measure to improve outcomes in these patients.

TABLE 2 Continued

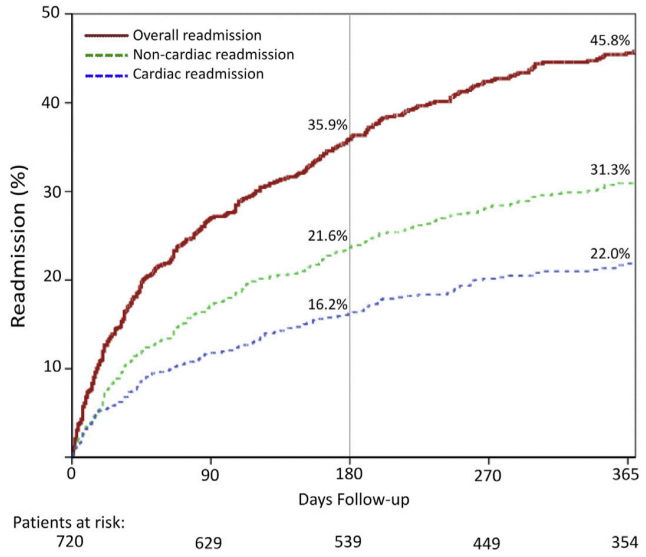
Causes of Readmission	Overall, 1 Year (n = 506)	Early, ≤30 Days (n = 115)	Late, 30-365 Days (n = 391)
Noncardiac causes	298 (58.9)	66 (57.4)	232 (59.3)
Respiratory	60 (11.9)	11 (9.6)	49 (12.5)
Pneumonia	29	6	23
Upper respiratory tract infection	17	3	14
COPD exacerbation or respiratory failure	9	1	8
Others	5	1	4
Infection	46 (9.1)	12 (10.4)	34 (8.7)
Access site	15	7	8
Genitourinary	11	1	10
Gastrointestinal	7	2	5
Bacteremia without endocarditis	4	0	4
Other	9	2	7
Bleeding	36 (7.1)	10 (8.7)	26 (6.7)
Gastrointestinal	29	8	21
Access site	2	1	1
Genitourinary	2	1	1
Others	3	0	3
Peripheral vascular event	26 (5.1)	7 (6.1)	19 (4.9)
Arterial limb event	15	5	10
Pulmonary thromboembolism	5	1	4
Vein limb event	3	0	3
Others	3	1	2
Cerebrovascular event	26 (5.1)	9 (7.8)	17 (4.3)
Ischemic cerebrovascular event	23	9	14
Intracranial bleeding	3	0	3
Traumatology	26 (5.1)	6 (5.2)	20 (5.1)
Fall	10	3	7
Fractures	12	2	10
Other	78 (15.4)	11 (9.6)	67 (17.1)

Values are n (%) or n.
COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement.

Cardiac arrhythmias are a well-known factor for rehospitalization after cardiac surgery (13,33), representing the second cause of cardiac readmissions after TAVR in the present study. Interestingly, tachyarrhythmias (mainly atrial fibrillation) accounted for two-thirds of such cases, whereas bradyarrhythmias were responsible for one-third of readmissions due to arrhythmic causes. These data suggest the extension of the atrial arrhythmia burden beyond the periprocedural period (34), and emphasize the importance of better establishing the predictors of late advanced atrioventricular block requiring pacemaker implantation after TAVR, especially in patients in whom conduction disturbances develop after the procedure (28,35,36). Importantly, although one-fourth of cardiac readmissions required an invasive procedure (mainly pacemaker implantation or coronary angiography), only a few patients required reintervention at the prosthesis level (balloon post-dilation, paravalvular leak closure, or implantation of a second valve in most cases). This is in accordance with previous studies showing the very low rate of reinterventions or structural failure associated with transcatheter prostheses up to 5-year follow-up (37).

PREDICTORS OF 30-DAY AND LATE HOSPITAL READMISSION POST-TAVR. The ability to identify those patients at higher risk of readmission after TAVR is a critical step for optimizing health care programs in a cost-efficient manner. Interestingly, the predictors of 30-day readmission were mainly related to periprocedural complications (bleeding events in particular) and treatment at hospital

FIGURE 2 Hospital Readmission Events Within the Year After TAVR



Kaplan-Meier curves showing the readmission events over time, overall, and according to the main reasons for readmission (cardiac/noncardiac). TAVR = transcatheter aortic valve replacement.

discharge, whereas the main factors associated with later rehospitalizations were patient comorbidities.

Periprocedural major bleeding events remain one of the most frequent complications of TAVR, and several studies have shown the high impact of such events on patient survival (26,27,38). It is therefore not surprising that this periprocedural complication predicted early readmissions in our study. Additionally, a lower hemoglobin level at hospital discharge also played an important role in early readmissions. In fact, anemia has been well recognized as an important risk factor for hospital readmission (39), and we previously showed that the vast majority of TAVR patients have some degree of anemia at hospital discharge (40). The interaction between low hemoglobin levels and heart failure decompensation as well as enhancement of the symptoms related to any bleeding episode may represent the most important pathophysiological links between anemia and early rehospitalization post-TAVR (41,42). Finally, a more intensive antithrombotic treatment consisting of a combination of anticoagulant and antiplatelet drugs was also associated with a higher risk of early readmissions. The use of such antithrombotic combination therapies has increased the risk of bleeding events after valve surgery, and its risks should be appropriately balanced against the potential benefits in this high-risk population (27). In summary, these results suggest that reducing periprocedural bleeding events, better management of anemia before hospital discharge, and decreasing the intensity of antithrombotic treatment (particularly in patients with high bleeding risks) may reduce the rates of early rehospitalization after TAVR. The efficacy of implementing programs directed at correcting such factors needs to be demonstrated in future studies.

TABLE 3 Predictors of Early (≤30 Day) Hospital Readmission After TAVR

	Univariable		Multivariable	
Predictors	Analysis, OR (95% CI)	p Value	Analysis, HR (95% CI)	p Value
Diabetes	1.46 (1.01–2.12)	0.043		
eGFR at hospital discharge, ml/min*	1.11 (1.02–1.22)	0.021		
Transfemoral approach	0.63 (0.43–0.90)	0.013		
Acute kidney injury (stages 1–3)	1.56 (1.05–2.31)	0.028		
Major or life-threatening bleeding	2.34 (1.55–3.55)	<0.001	2.41 (1.57–3.70)	<0.001
LVEF at hospital discharge, %†	1.11 (1.04–1.18)	0.002	1.08 (1.00–1.17)	0.042
Hemoglobin at hospital discharge, g/dl‡	1.26 (1.09–1.44)	0.002	1.19 (1.03–1.39)	0.019
Significant MR at hospital discharge	2.03 (1.25–3.28)	0.004		
Single or dual antiplatelet + anticoagulation therapy	1.85 (1.26–2.72)	0.002	1.62 (1.10–2.39)	0.014

*For each decrease of 10 ml/min. †For each decrease of 5%. ‡For each decrease of 1 g/dl.
CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation; OR = odds ratio; other abbreviations as in Tables 1 and 2.

The risk of late (>30 days) readmission after TAVR was mainly determined by the presence of atrial fibrillation, peripheral vascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, which have also been systematically found to be strong mortality risk factors in TAVR (6,22,23). Lindman et al. (8) also reported an independent association between major arrhythmia and late procedure-related or cardiac readmission. Interestingly, a lower mean gradient at baseline was a factor determining multiple readmissions in our study. Multidisciplinary evaluation of these patients is necessary not only in the patient-selection process, but also in post-procedure follow-up. These findings suggest that implication and evaluation in the immediate outpatient TAVR clinic by other specialized clinics (e.g., pulmonology, nephrology, geriatricians) will be essential to improve their outcomes. The complexity of the comorbidities of the current TAVR population may require a better selection process and closer follow-up.

CLINICAL IMPACT OF EARLY READMISSIONS POST-TAVR. Previous studies in the surgical field have identified early readmission as a risk factor for mortality at follow-up (43). Similar to these studies, our results also suggest an independent association between early readmission post-TAVR and poorer clinical outcomes. Apart from the negative consequences of hospitalization (e.g., risk of nosocomial infections), early readmission probably identifies a vulnerable group of patients with a higher risk of poorer outcomes in the coming months. Future efforts should be made to identify and enhance the post-discharge health care measures in this group of patients.

STUDY LIMITATIONS. This study was limited to 2 high-volume TAVR centers, and the results will need validation in a larger multicenter cohort of patients. However, readmission rates were similar to those recently reported in the TVT registry (6) and are likely representative of the global TAVR population. No event adjudication committee was available for this study. However, unlike most previous series reporting readmission rates on the basis of digital codes, the principal diagnosis for hospital readmission in our study was established on the basis of the final diagnosis at hospital discharge after a detailed medical record review. There was no systematic pre-procedural geriatric evaluation of the patients, and the impact of typical factors on this population such as frailty or cognitive impairment was not assessed.

CONCLUSIONS

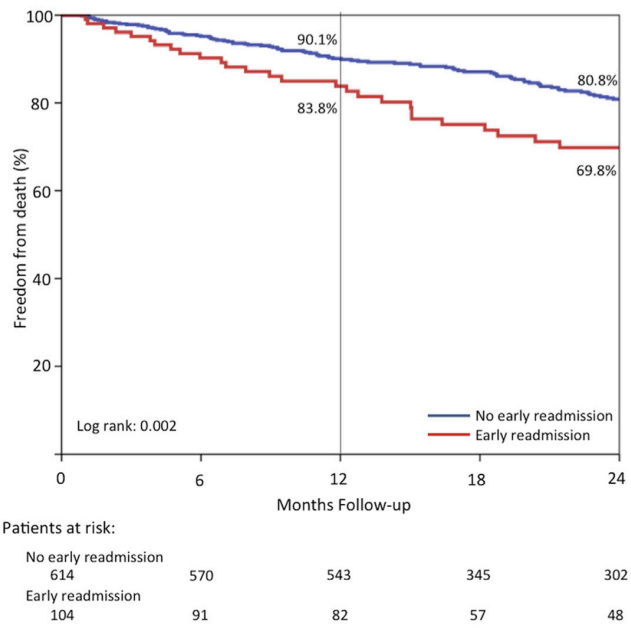
The readmission burden in TAVR patients is very high (almost 50% at 1 year), with almost one-fourth of the episodes occurring in the early (≤30 days) period after hospital discharge. Noncardiac causes led by respiratory, infection, and bleeding events accounted for nearly two-thirds of readmission episodes, whereas cardiac causes led by heart failure were responsible for the remainder of hospitalizations. Although periprocedural bleeding events, left ventricular ejection fraction, anemia, and intensive antithrombotic treatment were the main predictors of early readmissions, patient comorbidities (chronic obstructive pulmonary disease, peripheral vascular disease, atrial fibrillation, and renal dysfunction) were the main factors determining late readmissions. Early readmission was identified as an independent predictor of mortality at 2-year follow-up. These results delineate, for the first time, all types of readmission causes post-TAVR and reflect the real-world all-comer readmission burden in this population. In addition, they provide the rationale for implementing specific health care programs to reduce readmissions after TAVR. While waiting for the results of future randomized studies to determine the most effective strategies to reduce hospital

TABLE 4 Predictors of Late (30-365 Days) Hospital Readmission After TAVR

Predictors	Univariable Analysis, OR (95% CI)	Univariable p Value	Multivariable Analysis, HR (95% CI)	Multivariable p Value
COPD	1.46 (1.18–1.79)	<0.001	1.49 (1.21–1.84)	<0.001
Peripheral vascular disease	1.37 (1.11–1.70)	0.004	1.29 (1.04–1.61)	0.023
Previous cerebrovascular disease	1.30 (1.02–1.65)	0.034		
Atrial fibrillation (chronic or paroxysmal)	1.28 (1.04–1.57)	0.019	1.32 (1.06–1.63)	0.012
eGFR at hospital discharge, ml/min*	1.05 (1.01–1.09)	0.021	1.05 (1.01–1.09)	0.013
LVEF, %†	1.05 (1.02–1.09)	0.005		
Single or dual antiplatelet + anticoagulation therapy	1.26 (1.02–1.55)	0.032		

*For each decrease of 10 ml/min. †For each decrease of 5%.
Abbreviations as in Tables 1 through 3.

FIGURE 3 Early Hospital Readmission After TAVR and Mortality



Kaplan-Meier survival curves between 30-day and 2-year follow-up for all-cause mortality after TAVR, according to the occurrence of early (≤30 days) hospital readmission. TAVR = transcatheter aortic valve replacement.

TABLE 5 Predictors of Mortality (30 Days to 2 Years) After TAVR

Predictors	Univariable Analysis, HR (95% CI)	Univariable p Value	Multivariable Analysis, HR (95% CI)	Multivariable p Value
Atrial fibrillation	1.77 (1.24–2.53)	0.002	1.60 (1.11–2.30)	0.012
COPD	1.67 (1.14–2.42)	0.008	1.62 (1.10–2.38)	0.015
eGFR, ml/min*	1.09 (1.01–1.18)	0.036		
Hemoglobin at hospital discharge	1.15 (1.01–1.32)	0.040		
Acute kidney Injury	1.96 (1.34–2.87)	0.001	1.74 (1.17–2.60)	0.006
Significant MR at hospital discharge	2.56 (1.64–3.97)	0.001	2.20 (1.41–3.46)	0.001
Early (≤30 days) readmission	1.89 (1.25–2.87)	0.003	1.56 (1.02–2.39)	0.043

*For each decrease of 10 ml/min.
Abbreviations as in Tables 1 through 3.

readmission and associated costs, urgent measures are needed to reduce such a high readmission burden and maintain the cost-effectiveness of TAVR.

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PERSPECTIVES

WHAT IS KNOWN? Unplanned readmissions after initial cardiac intervention or hospitalization are frequent and associated with a significant impact on survival, patient quality of life, and health care costs.

WHAT IS NEW? Almost one-half of the patients undergoing TAVR were readmitted within 1 year. One-fifth were readmitted within the first month and multiple (≥2) readmissions were observed in more than one-third of the cohort. Approximately 60% of readmissions were secondary to noncardiac causes, and baseline comorbidities played an important role in delayed readmission.

WHAT IS NEXT? The high readmission burden observed in this population should be taken into account so that specific preventive measures and post-procedural management to reduce readmission rates and costs and improve quality of life after TAVR can be implemented.

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KEY WORDS aortic stenosis, bleeding events, readmission, rehospitalization, transcatheter aortic valve implantation, transcatheter aortic valve replacement

DISCUSIÓN

El rápido desarrollo del TAVR ha generado el surgimiento de múltiples dispositivos valvulares de implante transcatéter. Como se ha comentado, las dos válvulas con las que se tiene mayor experiencia clínica son la familia de válvulas balón-expandibles Edwards y la familia de válvulas autoexpandibles CoreValve. Ambos sistemas han demostrado excelentes resultados en términos de éxito del procedimiento, incidencia de complicaciones y resultados hemodinámicos a corto, medio y largo plazo (70,109,136). Por ello, se considera que los nuevos sistemas valvulares de implante transcatéter que acceden al mercado han de presentar, al menos, resultados equiparables a los de estas dos válvulas de avalada experiencia.

La válvula Portico (St Jude Medical, St Paul, MN, USA) está formada por un stent autoexpandible de nitinol en cuyo interior se despliegan 3 velos valvulares de pericardio bovino (137). El segmento anular de la válvula está recubierto por un manguito de pericardio porcino con el fin de constituir una zona de sellado y minimizar la incidencia de fugas a este nivel. La válvula es tratada con la tecnología anticalcificación Linx TM y procesada en una solución específica para su preservación. El catéter de liberación avanza por una guía de 0,035 mm y tiene un diámetro exterior de 18F en su extremo distal y de 12 F en su extremo proximal, por ello, precisa de un introductor arterial de 18F. La punta distal del sistema de liberación es atraumática y radioopaca para un mejor posicionamiento de la válvula. La válvula puede ser totalmente recapturada y reposicionada hasta que se ha liberado un 80-90% de su superficie. En ese punto, la porción anular del stent contacta en su totalidad con el anillo aórtico pudiéndose evaluar antes de su total liberación si la posición y la hemodinámica valvular son las adecuadas. Una vez desplegada la válvula, ésta está diseñada para funcionar a nivel anular, lo cual otorga una gran estabilidad hemodinámica durante la

liberación, sin necesidad de estimulación ventricular a alta frecuencia. La primera válvula Pórtico de la que se dispuso tenía un diámetro de 23 mm. El primer implante en humanos de esta válvula se llevó a cabo en 2012 (138). Actualmente se dispone de válvulas de 23, 25, 27 y 29 mm que permiten tratar a pacientes cuyo diámetro del anillo aórtico esté comprendido entre los 19 y los 27 mm.

Como característica diferencial con otros sistemas valvulares de implante transcatéter, cabe reseñar que las celdas del stent (o la distancia entre los struts del mismo) son más amplias que en otras válvulas. Este hecho permite un mejor sondaje de los ostiums coronarios si el paciente precisa posteriormente de la realización de una angiografía coronaria. Además, esta configuración permitiría también una mejor acomodación de los posibles nódulos de calcio son el fin de intentar minimizar la incidencia de fugas paravalvulares. Sin embargo, a este respecto, es preciso señalar que una mayor distancia entre los struts del stent implica también una menor cantidad relativa de metal, lo cual se traduce en una menor fuerza radial de la válvula y podría traducirse en una mayor incidencia de IAo residual. Por todo ello, consideramos de gran importancia, comparar los resultados hemodinámicos de esta válvula con los de otro sistema valvular ampliamente utilizado como la válvula balón-expandible Sapien XT. Para ello se emparejaron a 22 pacientes tratados mediante implante transcatéter de la válvula Portico de 23 mm con 40 pacientes tratados con la válvula SAPIEN XT de 23 mm, según los parámetros: área y diámetro medio del anillo aórtico por TC multidetector, FEVI, área de superficie corporal e índice de masa corporal

Como puede verse en el primer artículo que conforma la presente tesis, que constituyó el primer análisis comparativo entre la válvula Portico y otro dispositivo de implante transcatéter, en el ecocardiograma realizado a los 30 días del implante, no se encontraron diferencias estadísticamente significativas entre los dos dispositivos

estudiados en términos de gradiente residual, área valvular efectiva, ocurrencia de insuficiencia aórtica moderada o severa o incidencia de Desajuste Paciente-Prótesis (PPM). Aunque el estudio no tiene potencia estadística suficiente para detectar diferencias en el pronóstico clínico, no se objetivaron diferencias significativas en la ocurrencia de muerte, accidente cerebrovascular o necesidad de implante de marcapasos.

El hecho de que se evaluase únicamente un tamaño valvular (23mm) y de que el seguimiento clínico y ecocardiográfico fuese de 30 días, constituyen dos de las limitaciones más importantes de nuestro estudio. A este respecto, se ha publicado recientemente un estudio que incluye el seguimiento a un año de 57 pacientes tratados en Canadá con la válvula Portico entre marzo de 2012 y agosto de 2014(139). De estos 57 pacientes, 11 corresponden a pacientes incluidos en nuestro estudio comparativo con la válvula Sapien XT. La edad media de los pacientes fue de 80,8 ± 7,3 años y el STS de 7,7±5,7%. La distribución de los tamaños valvulares implantados fue la siguiente: 23 mm en 30 pacientes (52,6%), 25 mm en 12 pacientes (21,1%) , 27 mm en 11 pacientes (19,3%) y 29 mm en 4 (7%). Cuatro pacientes (7%) precisaron del implante de una segunda válvula. En tres de ellos, el implante de una segunda válvula se debió a la existencia de IAo severa tras el implante de la primera, probablemente a causa de que las fuerzas acumuladas durante la liberación de la válvula provocaron su desplazamiento una vez que ésta ya no era recapturable. En el cuarto caso, se implantó una segunda válvula por fallo mecánico de uno de los velos. Estos pacientes presentaron una alta mortalidad, y aunque los autores señalan que el inicio de la experiencia con un nuevo dispositivo suele asociarse a una incidencia mayor de implante de segunda válvula (140), este es un dato que deberá ser seguido en series mayores.

La supervivencia fue del 96,5% a 30 días y del 84,2% al año. Se documentaron 3 accidentes cerebrovasculares incapacitantes (5,3%) y 5 pacientes necesitaron el implante de un marcapasos definitivo tras el procedimiento (8,8%). Con respecto a los resultados hemodinámicos, en el ecocardiograma a 30 días el gradiente transprotésico medio fue de 12,7±8,5 mm Hg y se objetivó IAo moderada o severa en dos pacientes (3,6%). En el ecocardiograma al año, se registró IAo moderada o severa en 4 pacientes (10,3%). Como se deduce de estas cifras y de las resultantes de nuestro estudio comparativo, la incidencia de IAo residual no difiere significativamente de la documentada en los dispositivos de segunda generación. Sin embargo, en el escenario actual, en el que la mayoría de los centros implantan dispositivos de tercera generación como la válvula Sapien 3 y la válvula Evolut R, estas cifras podrían no ser tan competitivas no tanto en referencia a la incidencia de IAo moderada-severa, sino también respecto a la incidencia de IAo leve. Aunque aún no existe certeza al respecto, varios estudios señalan que la presencia de IAo residual aun en grado leve, podría tener repercusiones pronósticas (125). En nuestro estudio, los pacientes sin ningún tipo de IAo residual fue del 38%, mientras que recientes registros con las válvulas Evolut R y Sapien 3, arrojan datos superiores al 50% y al 70%, respectivamente (141,142).

En el estudio de Perlman y colaboradores, en un ecocardiograma de control al año se detectó la presencia de trombo valvular en un paciente asintomático. El gradiente transprotésico medio era de 6 mm de Hg y la IAo paravalvular que había sido descrita como “trivial” no sufrió cambios. Ni en nuestro estudio ni el anteriormente citado de Perlman se realizo ecocardiograma transesofágigo o TC MC de forma sistemática. Pese a que las experiencias iniciales habían sido exitosas y a que ningún estudio había demostrado deterioro de la hemodinámica valvular, St Jude Medical detuvo temporalmente todo el programa de la válvula Portico en septiembre de 2014. Esta

decisión se llevó a cabo tras detectarse movilidad reducida en los velos de las válvulas implantadas en pacientes que participaban en el estudio Portico Re-sheathable Transcatheter Aortic Valve System U.S. Investigational Device Exemption (PORTICO IDE) (ClinicalTrials.gov: 02000115). Dicho estudio aleatorizado pretendía comparar la evolución clínica y hemodinámica de los pacientes tratados con la válvula Portico en relación con aquellos tratados con otros sistemas de implante trasncatéter más establecidos como la válvula Sapien XT y la válvula CoreValve.

Por la trascendencia que ha tenido posteriormente, creemos que es importante comentar estos hallazgos que fueron publicados por Makkar y colaboradores en New England Journal of Medecine en noviembre de 2015 (143). Según lo especificado en el estudio Portico IDE, se realizó TC 4D en un subgrupo de pacientes para valorar el estado del stent de la válvula 30 días después del implante de la misma. Se encontraron defectos en la movilidad de uno de los velos en un paciente que había sufrido un ACV tras el procedimiento de TAVR y en otro paciente asintomático. Estos hallazgos motivaron un cuidadoso análisis de los estudios ecocardiográficos y de TC 4D y que se pusieran en marcha dos registros destinados a evaluar la movilidad de los velos tras un procedimiento de TAVR o de SAVR: los registros RESOLVE (*Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation*) y SAVORY (*Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography*). De los 55 pacientes a los que se les realizó TC en el estudio Portico IDE se detectó alteración en la movilidad de, al menos 1 de los velos, en 22 pacientes (**Figura 5**). Estos 22 pacientes constituían el 40% de los incluidos hasta ese momento en el estudio y representaban el 43% de los tratados con la válvula Portico (16 de 37), el 43% de los tratados con la válvula Sapien XT (6 de 14) y el 0% de los tratados con la válvula CoreValve (0 de 4). Se realizó un ETE en 10

de los 22 pacientes una mediana de 9 días tras el TC, que confirmó en el 100% de los casos, la presencia de una masa hiperecogénica situada en el lado aórtico de la válvula, que impedía la normal excursión del velo. La prevalencia de alteraciones en la movilidad de los velos fue inferior en los pacientes tratados con warfarina en rango terapéutico (INR>2) en el momento de la realización del TC que en aquellos que no recibían anticoagulación o que lo hacían en rango subterapeútico (0 Vs 51% p=0,007). De igual forma, también fue inferior en pacientes anticoagulados con respecto a los pacientes que recibían doble terapia antiagregante (0% Vs. 55% p=0,01). Otro hecho que apoya la teoría de que los defectos en la movilidad de los velos se deben a trombosis valvular es la diferente evolución en función del tratamiento anticoagulante instaurado tras este hallazgo. Así, a los 6 meses se realizó TC de control a 21 pacientes, de ellos, el defecto en la movilidad se había resuelto en el 100% de los que recibieron tratamiento anticoagulante pero sólo en 1 de los pacientes que no recibió anticoagulación (p<0,001).

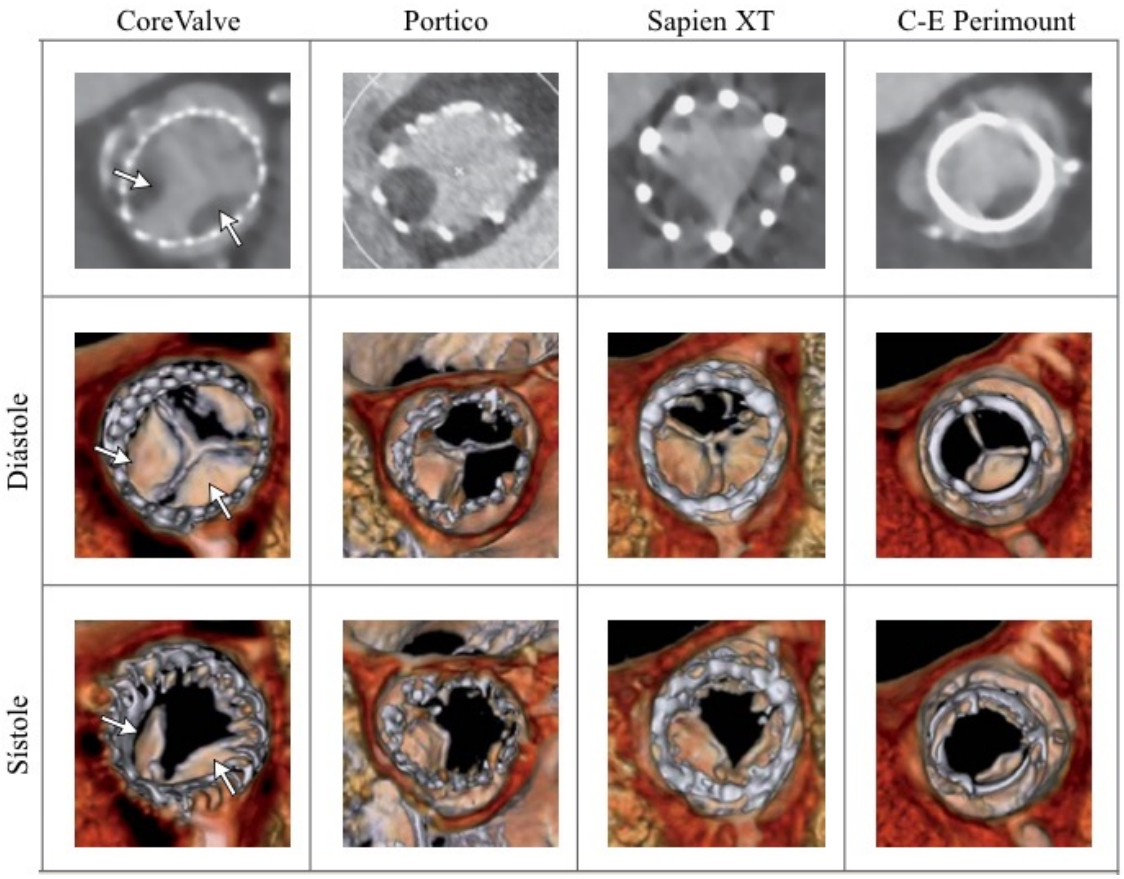

Figura 5: Alteraciones en la movilidad de los velos valvulares detectadas mediante TC en diferentes tipos de bioprótesis (Adaptado de Makkar et Al. (143)).

Los resultados de los registros RESOLVE (n=657 pacientes) y SAVORY (n=274 pacientes) han sido publicados recientemente y confirman y amplían la información aportada por el estudio Portico IDE (144). De los 890 pacientes con TC interpretable (96% de los incluidos), 752 habían recibido una válvula de implante transcatéter y 138 una válvula de implante quirúrgico. La mediana de días desde el implante hasta la realización del TC fue de 82 días tras TAVR y de 163 días tras SAVR. Los pacientes tratados mediante cirugía eran significativamente más jóvenes y con menores comorbilidades como HTA, insuficiencia renal crónica, hiperlipemia e insuficiencia cardiaca. Se detectó movilidad reducida de, al menos, un velo en el 12% de los pacientes y éste hallazgo fue más frecuente en pacientes tratados mediante TAVR (101 de 752 pacientes tratados con válvulas transcatéter [13%] Vs. 5 de 138 pacientes

tratados con válvulas quirúrgicas [4%] p=0,001). En el análisis multivariado, el implante transcatéter (vs quirúrgico), la edad elevada, la baja FEVI y la ausencia de anticoagulación, se asociaron de forma independiente con una mayor prevalencia de alteraciones en la movilidad de los velos. Así, la prevalencia de esta alteración fue menor entre los pacientes que recibieron anticoagulación (8 [4%] de 224) que entre aquellos que recibían doble terapia antiagregante (31 [15%] de 208; p<0,0001), antiagregación en monoterapia (63 [16%] de 405; p<0,0001) o aquellos que no estaban recibiendo anticoagulantes (98 [15%] de 666, p<0,0001). No hubo diferencias entre los pacientes que recibían anticoagulación con warfarina y los que recibían nuevos anticoagulantes (p=0,72). Se realizó TC durante el seguimiento en 58 de los pacientes con reducción en la movilidad de los velos. La movilidad de los velos se normalizó en el 100% de los pacientes que recibieron anticoagulación durante 3 meses (n=36) y sólo en el 9% de los pacientes que no fueron anticoagulados (p<0,0001). Tras la restauración de la dinámica valvular, los defectos en la movilidad de los velos recurrieron en 4 de los 8 pacientes en los que se retiró la anticoagulación y en ninguno de los 15 pacientes que continuaron con el tratamiento anticoagulante (p=0,008, mediana de tiempo desde la discontinuación al nuevo TC de control: 164 días). Especialmente interesante son las consecuencias clínicas y hemodinámicas que se encuentran en los pacientes de estos registros tras la detección de esta anomalía en el TC 4D. Durante un seguimiento medio de 540 ± 413 días no se registraron diferencias estadísticamente significativas en las tasas de muerte, infarto de miocardio o ACV. Sí se encontró una mayor incidencia de AIT (6% Vs. 1% p=0,0005) y del compuesto de AIT o ACV (10% Vs. 3% p=0,001) en los pacientes con defectos en la movilidad de los velos. Estas diferencias se mantuvieron incluso cuando se excluyeron los AIT ocurridos en las 72 primeras horas, los cuales podrían atribuirse a aspectos relacionados con el procedimiento. Con respecto

a los resultados hemodinámicos, los pacientes con disminución de la movilidad de alguno de los velos presentaron gradientes medios significativamente más altos (13,8 Vs 10,4 mm Hg p=0,004) y presentaron, con más frecuencia, tanto gradientes superiores a 20 mm Hg (16% Vs. 6% p=0,0002), como un incremento superior a 10 mm de Hg en el momento del TC con respecto a la determinación post-implante (15% Vs 1% p<0,0001).

Interesantemente, los resultados hemodinámicos de este estudio serían concordantes con los del estudio que representa el segundo artículo de la presente tesis doctoral (145). En él, se estudió la incidencia de deterioro de la hemodinámica valvular (DHV), definida como un aumento en el gradiente medio de al menos 10 mm de Hg en un ecocardiograma durante el seguimiento respecto al ecocardiograma post-TAVR, en una cohorte de más de 1500 pacientes tratados en 10 centros de Europa y América. La incidencia de DHV fue del 2,8% durante el primer año y del 4,5% durante un seguimiento ecocardiográfico medio de 20 meses. En el análisis multivariante, los factores independientemente asociados con mayor incidencia de DHV fueron: un mayor índice de masa corporal, el implante de válvulas pequeñas (≤23mm), el antecedente de SAVR previo (procedimientos ViV) e, interesantemente, la ausencia de tratamiento anticoagulante al alta. Así, la incidencia de DHV fue del 1,9% entre los pacientes que recibieron tratamiento anticoagulante y del 5,6% entre los pacientes no anticoagulados, apoyando la teoría de que la trombosis subclínica es uno de los mecanismos fisiopatológicos que subyace en el desarrollo de DHV. En nuestro estudio no se encontraron diferencias estadísticamente significativas en el pronóstico clínico entre los pacientes con y sin DHV medido en términos de ocurrencia de muerte, muerte de origen cardiovascular o ACV.

Usando esta misma definición de DHV, Vemulapalli y colaboradores estudiaron a los pacientes incluidos en el *Transcatheter Valve Therapy (TVT) registry* (Vemulapalli et Al., ACC 2016, Chicago). Así, partiendo de una cohorte de más de 10.000 pacientes, encontraron una incidencia de DHV del 2,1% a los 30 días postimplante. Se dispuso de ecocardiograma al año de 3175 pacientes con una incidencia de DHV del 2,5% entre 30 y 365 días. En concordancia con nuestros resultados, la ausencia de anticoagulación al alta, un mayor IMC, el uso de válvulas de 23 mm y los procedimientos "valve in valve" se asociaron con mayor incidencia de VHD. Otros factores asociados con un aumento en el gradiente medio >10 mm Hg fueron: el sexo masculino, la enfermedad pulmonar obstructiva severa, un mayor gradiente medio al alta y el PPM severo. Tras un seguimiento clínico de 18 meses, no se encontraron diferencias estadísticamente significativas en términos de muerte, ingreso por insuficiencia cardiaca, IM, ACV o necesidad de reintervención entre los pacientes que cumplían criterios de DHV y los que no.

Tanto nuestro estudio como el de Vemulapalli sugieren que la trombosis valvular podría ser uno de los causantes de la DHV, sin embargo, ambos estaban encaminados, no a valorar este hallazgo sino a detectar cambios en la hemodinámica valvular por lo que el método diagnóstico principal fue el ETT. Además del ya citado estudio Portico I y de los registros SAVORY y RESOLVE, han sido publicados otros estudios destinados a valorar con técnicas de imagen más avanzadas, hallazgos sugerentes de trombosis tras TAVR. De ellos, citaremos seguidamente los más importantes.

Leetmaa y colaboradores estudiaron mediante TC 4D a 140 pacientes tratados mediante implante de la válvula Sapien XT(146). El estudio de imagen se realizó entre 1 y 3 meses después del implante. Se encontraron hallazgos sugerentes de trombosis

valvular, definidos como una masa de baja atenuación unida a uno de los velos o como un engrosamiento difuso de ≥1 mm de los mismos, en 5 pacientes (4%). De ellos, 4 pacientes (80%) se encontraban asintomáticos y tenían un ETT normal, si bien los hallazgos fueron evidentes en el ETE en todos los pacientes.

En un estudio posterior con 156 pacientes consecutivos tratados con la válvula Sapien 3, Pache y cols estudiaron la incidencia de engrosamiento de los velos mediante la realización de TC una mediana de 5 días después del implante valvular (147). La alteración sugerente de trombosis se definió como una imagen hipoatenuada de engrosamiento de al menos un velo visible en, al menos, dos proyecciones. Dicho hallazgo fue encontrado en 16 pacientes (10,3%), todos ellos se encontraban asintomáticos en el momento de la realización del TC. Ninguna característica basal ni relacionada con el procedimiento se asoció con una mayor incidencia de esta alteración en el TC. En comparación con los pacientes en los que no se detectó alteración en el grosor de los velos, estos pacientes presentaban un discreto pero significativo aumento en el gradiente medio (14,9 ±5,3 Vs 11,6 ± 3,4 mm Hg p=0,026). Se realizó TC de control en 13 de los 16 pacientes (81%) que evidenció resolución de la imagen de engrosamiento en todos los pacientes que habían sido tratados con antocoagulación+clopidogrel y persistencia de la misma en un paciente que había seguido tratamiento únicamente con aspirina. Este estudio contó con un seguimiento clínico (mediana de 228 días tras el procedimiento) durante el cual un paciente falleció de muerte no cardiovascular a los 8 meses y otro presentó disnea clase II de la NYHA, los restantes 14 pacientes se encontraban asintomáticos. No se detectaron eventos isquémicos ni de sangrado.

Otro importante estudio en válvulas balón-expandibles es el desarrollado por Hansson y colaboradores (148). En él se estudiaron 460 pacientes consecutivos tratados

con las válvulas Sapien XT o Sapien 3, de los cuales en 405 se realizó TC, ETT y ETE entre el primer y el tercer mes tras el implante. La definición de engrosamiento e hipoatenuación de los velos fue similar a la utilizada en el estudio de Pache anteriormente descrita. La incidencia de trombosis valvular fue del 7% (28 pacientes) de los cuales el 82% se encontraban asintomáticos y sólo 5 (18%) presentaron síntomas. En el análisis multivariado los factores que se asociaron con una mayor incidencia de trombosis valvular fueron la ausencia de anticoagulación (Riesgo Relativo: 5,46; Intervalo de Confianza 95%: 1,68-17,7) y el implante de válvulas de 29mm (RR: 2,89; IC 95%: 1,44-5,80). En el momento del diagnóstico el gradiente transprotésico medio fue superior entre los pacientes que cumplían criterios de trombosis valvular (10 ± 7 Vs 8 ± 3 mm Hg p=0,03). Tras la instauración de tratamiento con warfarina, las imágenes sugerentes de trombosis valvular se resolvieron en el 85% de los casos. No se objetivaron diferencias significativas en términos de mortalidad al año entre los pacientes que cumplían criterios de trombosis valvular y los que no.

El último de los grandes estudios publicados sobre trombosis valvular en TAVR incluye pacientes tratados con diferentes tipos de prótesis trasncatéter (149) y siguió una metodología distinta a los mencionados anteriormente, pero quizá más cercana a las tendencias clínicas actuales. En este estudio, que incluyó a 642 pacientes, se programó un seguimiento clínico y mediante ETT a los 30 días, 6 meses y posteriormente, anualmente tras un procedimiento de TAVR. Dado que no se quiso estudiar la trombosis subclínica sino aquella que tuviese manifestaciones clínicas o ecocardiográficas, se realizó un ETE a todos los pacientes que referían empeoramiento de sus síntomas y a aquellos que mostraban un aumento de gradientes. Aunque no se contemplaba en el protocolo inicial, el estudio de estos pacientes con sospecha clínica o ecocardiográfica de trombosis se completó también con TC. Se consideró que un

paciente cumplía el objetivo primario de trombosis valvular si cumplía uno de los dos siguientes criterios: 1) disfunción valvular (gradiente transvalvular medio> 20 mm Hg, reducción del área valvular aórtica a <1,2 cm^2 o IAo al menos moderada de nueva aparición) secundaria a trombosis diagnosticada por respuesta a terapia anticoagulante o por hallazgos típicos en la modalidad de imagen correspondiente (ETE o TC); 2) masa móvil sospechosa de trombo detectada en la válvula en ausencia de infección, independientemente de la ocurrencia o no de disfunción valvular. La incidencia de trombosis valvular fue del 2,8% (18 pacientes). Es importante resaltar que ningún paciente en tratamiento anticoagulante crónico cumplió los criterios diagnósticos de trombosis valvular (p<0,0001). Así, teniendo en cuenta que, alrededor del 40% de los pacientes fueron dados de alta con anticoagulación, la verdadera incidencia de trombosis valvular entre los pacientes no anticoagulados fue del 4,8%. Dicho diagnóstico fue más frecuente en pacientes tratados con prótesis balón-expandibles (Odds ratio: 3,45; IC 95%: 1,22–9,81; p=0,01) y en procedimientos ViV (Odds ratio: 5,93; IC 95%: 2,01–17,51; p=0,005). A este respecto es preciso señalar que todos los casos de trombosis en válvulas CoreValve se dieron en procedimientos ViV. El gradiente transvalvular medio en pacientes con criterios de trombosis fue de 34 ± 14 mm Hg y se encontró imagen de hipoatenuación y engrosamiento de algún velo en todos los pacientes (n=9) con TC interpretable. Con respecto a la presentación clínica, la mayoría de los pacientes no presentaron empeoramiento de síntomas mientras que 7 pacientes (38,9%) describieron empeoramiento de su disnea y otro paciente presentó ACV 21 meses después del procedimiento. Los niveles séricos de NT-proBNP se encontraron más elevados en estos pacientes. Todos los pacientes con diagnóstico de trombosis valvular fueron tratados con anticoagulación, lo cual normalizó el gradiente transvalvular medio hasta los niveles basales en todos los pacientes excepto en uno, el

cual fue diagnosticado 3 años después del implante (se detectó reducción de los gradientes pero no hasta los valores basales). La mediana de tiempo desde el implante hasta el diagnóstico de trombosis fue de 181 días y desde la instauración del tratamiento anticoagulante hasta la normalización del gradiente, de 14 días. No se registró recurrencia de la trombosis valvular en ningún paciente, si bien dos de ellos presentaron reelevación transitoria del gradiente medio tras la retirada temporal de la anticoagulación. En este estudio no se reportan objetivos de pronóstico clínico, si bien los autores hacen referencia a que ningún paciente falleció por consecuencia directa de la trombosis valvular.

Son varias las conclusiones y también los interrogantes que se derivan de todos los estudios anteriormente citados:

En primer lugar, podemos inferir que la trombosis valvular post-TAVR engloba un amplio espectro de enfermos que incluye: pacientes asintomáticos con gradientes normales y un hallazgo casual en pruebas avanzadas de imagen (mayoritariamente TC), pacientes asintomáticos con gradientes transprotésicos aumentados y pacientes con gradientes elevados y manifestaciones clínicas entre las que se encontrarían la insuficiencia cardiaca y los eventos tromboembólicos (150). A este respecto la incidencia variaría entre el 10-15% de las alteraciones en la movilidad de los velos detectadas por TCMC hasta el 0,6-3% de los pacientes que presentan síntomas de IC franca asociados a trombosis valvular (151). Así pues, parece necesario que los nuevos documentos de consenso incluyan una definición y algoritmo precisos para el diagnóstico tanto de trombosis como de degeneración valvular post-TAVR.

En segundo lugar, dado que parece haber un periodo de trombosis subclínica en el que el ETT es insuficiente para detectar la trombosis valvular, cabe preguntarse si la realización de TCMC debe ser incorporada en el seguimiento rutinario de los pacientes

tratados mediante TAVR. Dado que la repercusión de este hallazgo sobre los eventos clínicos y la durabilidad de la prótesis a largo plazo aún no ha sido bien determinada, consideramos que la carga de evidencia actual no justificaría la realización rutinaria de esta prueba. Además, es preciso tener en cuenta que la población sometida a TAVR presenta una alta incidencia de IRC y que se han descrito artefactos en hasta el 20-30% de los pacientes sometidos a TCMC (152). Aunque las guías de práctica clínica no han emitido una recomendación al respecto, los expertos sugieren un enfoque pragmático que podría ser similar al llevado a cabo por Jose y colaboradores en el estudio anteriormente mencionado (149,153). Así pues, sería preciso un seguimiento clínico y eocardiográfico estrecho de todos los pacientes y en especial de aquellos con factores identificados como de riesgo para trombosis valvular (Ej pacientes sometidos a procedimientos ViV). El TC se llevaría a cabo cuando exista sospecha clínica (empeoramiento de síntomas) o ecocardiográfica (aumento de gradientes) de trombosis valvular. Si los hallazgos ecocardiográficos y de TC son sugerentes de trombosis, y el perfil de riesgo individual del paciente así lo permite, estaría indicado el inicio temprano de terapia anticoagulante.

En tercer lugar, y de forma más importante, emerge el interrogante de si es preciso recomendar, de forma generalizada, un periodo de anticoagulación tras TAVR. Si hacemos la analogía con los pacientes tratados de forma quirúrgica, las guías actuales recomiendan tratamiento anticoagulante durante los 90 días posteriores al implante quirúrgico de una bioprótesis (44,66). Estas recomendaciones se basaron en varios estudios observacionales que mostraron un menor riesgo de complicaciones tromboembólicas en pacientes tratados con warfarina(154,155). Sin embargo, el riesgo/beneficio de la terapia anticoagulante después del implante quirúrgico de una bioprótesis sigue siendo controvertido y otros autores sugieren que sólo los pacientes de

alto riesgo trombótico se beneficiarían del tratamiento con antagonistas de la vitamina K (156). A este respecto, dado que la trombosis valvular quirúrgica era un hecho inusual cuya incidencia se estimaba, mayoritariamente, en base a la necesidad de reoperación, los estudios disponibles hasta la fecha no han tenido potencia suficiente para determinar con exactitud ni el tipo ni la duración de la terapia trombótica post-SAVR. Con respecto a los pacientes tratados mediante TAVR, las guías europeas de 2012 recomiendan doble tratamiento antiagregante tras el procedimiento sin especificar la duración del mismo (antiagregación simple + anticoagulación para los pacientes con indicación de esta última)(44). La reciente actualización de las guías americanas, mantiene la indicación de aspirina y clopidogrel durante 6 meses tras TAVR con nivel IIb-C y se hace eco de los estudios que hemos mencionado anteriormente, recomendando anticoagulación durante al menos 3 meses, con INR objetivo de 2.5 en pacientes con bajo riesgo de sangrado (Nivel IIb-B)(66). En referencia a la indicación de doble antiagregación, es preciso recordar que se trató inicialmente de una indicación empírica, probablemente, resultante de equiparar el implante de bioprótesis montadas sobre un stent metálico con el implante de stents intracoronarios. Pese a esta recomendación, ninguno de los estudios hasta la fecha muestran menor incidencia de trombosis valvular o de deterioro de la hemodinámica en pacientes doblemente antiagregados. Además, se han presentado recientemente los resultados del estudio ARTE, los cuales desaconsejarían esta práctica (157). En este estudio se aleatorizaron 222 pacientes a recibir aspirina o aspirina+clopidogrel durante los 3 meses posteriores al implante de una válvula balón-expandible. En un seguimiento a 3 meses, se objetivó una mayor incidencia de sangrados graves o potencialmente mortales en el grupo de doble antiagregación (10,8% vs. 3,6% p=0,038), así como una tendencia a mayor ocurrencia del objetivo compuesto de muerte, IM, ACV/AIT y sangrado mayor (15,3%

Vs. 7,2% p=0,065); sin embargo, no se objetivaron diferencias en la ocurrencia de muerte (6,3% doble Vs. 3,6% monoterapia p=0,37) o del objetivo compuesto de ACV o AIT (2,7% doble Vs. 0,9% monoterapia p=0,31). Sin duda, los estudios aleatorizados que se encuentran actualmente en marcha tanto con warfarina como con nuevos anticoagulantes (**Tabla 5**), aportarán una información muy importante sobre la necesidad de indicar, sistemáticamete, un periodo de anticoagulación tras un procedimiento de TAVR.

Por último, otra de las cuestiones principales que se derivan de los estudios que hemos mencionado es si los pacientes tratados mediante TAVR con antecedentes de sustitución quirúrgica de la válvula aórtica con una bioprótesis (procedimientos ViV) presentan una evolución hemodinámica diferente. Según las últimas guías de práctica clínica, los procedimientos de TAVR ViV estarían indicados en pacientes sintomáticos con disfunción de una bioprótesis aórtica considerados por el Heart Team como de riesgo quirúrgico alto o inasumible (Clase IIa-Nivel B)(66). Sin embargo, como comentábamos, siguen existiendo dudas importantes respecto al resultado hemodinámico de estos procedimientos.

Estudio	Diseño	N	Tratamientos Analizados	Objetivos Primarios
ATLANTIS (NCT02664649)	Aleatorizado (pre-TAVR)	1509	Estrato 1 (indicación ACO): tratamiento habitual Vs Apixaban 5mg/12h 6 meses. Estrato 2 (no indicación ACO): tratamiento habitual (DTA/MTA) Vs Apixaban 5mg/12h 6 meses.	MACE: muerte, IM, ACV/AIT, embolismo sistémico, trombo protésico o intracardiaco, TEP, TVP. Seguridad: sangrado mayor.
AVATAR (NCT02735902)	2 estratos Aleatorización 1:1 por estrato	170	AVK (INR 2-3) 12 meses Vs. AVK (INR 2-3) + ASA (75-100 mg/24h) 12 meses	Compuesto: muerte, IM, ACV, trombosis valvular, hemorragia ≥ 2 (escala VARC)
GALILEO (NCT02556203)	Aleatorizado 1:1	1520	Rivaroxabán 10mg/24h + ASA 75-100 mh/24h (3 meses), luego Rivaroxabán 10mg/24h (12-24 meses) Vs DTA 3 meses, luego ASA 75-100 mg/24h (12-24 meses)	MACE: muerte, IM, ACV/AIT, embolismo sistémico, trombosis protésica TEP, TVP. Seguridad: sangrado mayor, que compromete la supervivencia o causa discapacidad.
POPular-TAVI (NCT02247128)	Aleatorizado Cohorte A/B: pacientes sin /con indicación de ACO	1000	Cohorte A: ASA (<100mg/24h) Vs DTA 3 meses, luego ASA hasta 12 meses. Cohorte B: Warfarina (INR 2) Vs Warfarina (INR 2) + Clopidogrel 75/24h 3 meses, luego Warfarina hasta 12 meses.	Seguridad: ausencia de toda complicación hemorrágica. Objetivos coprimarios: ausencia de sangrado no relacionados con el procedimiento.
REAC-TAVI (NCT02224066)	Randomizado según las URP	60	URP≥208: Ticagrelor 90/12h Vs DTA 3 meses. URP<208: DTA 3 meses.	Supresión de la reactividad plaquetaria residual medida por VerifyNow $P2Y_{12}$ a los 3 meses.
Frequency of Reduced Leaflet Motion After SAVR and TAVR (NCT02696226)	Piloto, aleatorizado	100 (TAVR/ SAVR)	Warfarina (INR 2-3) + Clopidogrel 75/24h (3 meses), luego DTA (3 meses), luego ASA 81 mg/24h (indefinidamente) Vs. DTA (6 meses), luego ASA 81 mg/24h (indefinidamente)	Impacto de la anticoagulación periprocedimiento en la frecuencia de disminución en la movilidad de los velos medida por TC 4D 4-6 semanas tras SAVR y TAVR.
Inflammation and Thrombosis in Patients With Severe Aortic Stenosis After TAVR (NCT02486367)	Aleatorizado, no ciego	60	Carga de 600 mg de Clopidogrel, luego Clopidogrel 75mg/24h Vs Carga de 180 mg de Ticagrelor, luego Ticagrelor 90/12h 1 mes.	Reactividad plaquetaria medida por el test VerifyNow (en URP) Objetivo secundario: % de CD14+ y CD16+ respecto al total de monocitos en citometría de flujo.

Tabla 5: Principales estudios registrados evaluando terapias antitrombóticas post-TAVR (Adaptado de Puri et Al. (153)). Abreviaturas: ACO: Anticoagulación Oral; ACV: Accidente Cerebrovascular; AIT: Accidente Isquémico Transitorio; AVK: Antagonistas Vitamina K; DTA: Doble Terapia Antiagregante; IM: Infarto de Miocardio; MACE: Eventos Cardiovasculares Mayores; MTA: Monoterapia Antiagregante; SAVR: Reemplazo Quirúrgico de Válvula Aórtica; TAVR: Reemplazo Transcatéter de Válvula Aórtica; TC: Tomografía Computerizada; TEP: Tromboembolismo Pulmonar; TVP: Trombosis Venosa Profunda; URP: Unidades de Reactividad Plaquetaria.

El objetivo del tercer artículo que conforma la presente tesis es recopilar la información más relevante disponible en la literatura sobre los procedimientos ViV, haciendo especial hincapié en los aspectos relacionados con la preparación del procedimiento y la hemodinámica valvular (158). Así, tras analizar todas las series publicadas hasta ese momento, se encontró que el gradiente transvalvular medio tras un procedimiento de TAVR ViV (incluyendo diversos tipos de válvulas) fue de 15,5 mm Hg. Este valor es significativamente mayor que el descrito tras TAVR en válvulas nativas (usualmente menor o en torno a 10 mm Hg). Se cree que, en estos procedimientos, los gradientes residuales más elevados puede deberse a la combinación de cierto grado de PPM tras el SAVR (sobre todo en pacientes tratados con válvulas quirúrgicas pequeñas) y a cierta infraexpansión de la válvula transcatéter provocada por un compromiso de espacio debido a la válvula quirúrgica previamente implantada(159). La incidencia de PPM también fue elevada, describiéndose una tasa global de PPM severo (definido como un área valvular efectiva < 0,65 cm^2/m^2) del 32,1%. La mortalidad media a los 30 días de las series publicadas fue del 8%. Aunque en el momento de la publicación de nuestra revisión había pocos estudios publicados con resultados a largo plazo, la mortalidad media al año se estimó en el 15,1%. La tasa de las principales complicaciones fue la siguiente: mal posicionamiento o embolización de la válvula: 12,4%; ACV: 1,4%; obstrucción coronaria: 2,2%; necesidad de implante de marcapasos: 7,4%. Aunque la incidencia de obstrucción coronaria y de mal posicionamiento de la válvula fue mayor que en TAVR sobre válvulas nativas, la necesidad de implante de marcapasos fue menor que la descrita hasta entonces, probablemente por cierta función de contención de la válvula quirúrgica previamente implantada y por la tendencia a realizar implantes más altos en estos pacientes.

El creciente número de enfermos con fallo de bioprótesis quirúrgicas tratados mediante TAVR hace que recientemente se hayan publicado dos importantes series que reportan resultados similares en este tipo de pacientes. Así, en los 337 pacientes tratados con la válvula Sapien XT e incluidos en el *PARTNER 2 Valve-in-Valve Registry* se objetivó un gradiente transprotésico medio de 17,7 mm Hg (RIQ: 16,2-19,1) a los 30 días y de 17,6 mm Hg (IC 95%: 16,2-19,1) al año postimplante (160). Aunque en todos los tamaños de válvula quirúrgica se evidenció una disminución significativa del gradiente medio y una ganancia significativa de área valvular efectiva, la incidencia de PPM severo (global del 58,4%) y de gradientes residuales >20 mm Hg al alta (incidencia global del 34,3%) fue diferente en función del diámetro interno de la válvula quirúrgica y del tamaño de la válvula transcatéter implantada. Las válvulas quirúrgicas con un diámetro interno real ≤ 20mm se asociaron con más frecuencia con gradientes medios al alta >20 mm Hg (p=0,0042) y con PPM severo (p<0,0001); así como también el implante de prótesis transcatéter ≤ 23 mm (p=0,0003 y p<0,0001, respectivamente). Aunque la ocurrencia de PPM no se asoció con mayor mortalidad al año (p=0,86), la persistencia de gradientes >20 mm Hg sí lo hizo (HR 2,27 [IC 95%: 1,16-4,46; p=0,014]. Es preciso señalar que en este estudio no se aportan datos respecto al PPM postquirúrgico, previo al procedimeinto ViV, si bien se considera que la existencia de un PPM significativo podría contribuir de forma significativa a un importante aumento de gradientes post-TAVR(161). En este estudio la mortalidad a los 30 días fue del 2,7%, con cifras al año similares a las descritas en estudios previos (12,4%).

El otro gran estudio de TAVR en ViV hace referencia a pacientes tratados con prótesis autoexpandibles. En los 227 pacientes incluidos en el *CoreValve US Expanded Study* con fallo de bioprótesis previa, se evidenció un gradiente trasnvalvular medio de 17 ± 8,8 mm Hg a los 30 días y de 16,6 ± 8,9 mm Hg al año del procedimiento de

TAVR (162). Los factores que se asociaron significativamente con gradientes altos al alta (gradiente medio ≥ 20 mm Hg) fueron el tamaño pequeño de la válvula quirúrgica (<23mm), la estenosis como modalidad de fallo de la bioprótesis y la presencia de PPM de la válvula quirúrgica (p<0,001 para todos los factores). En este estudio, sin embargo, la presencia de gradientes elevados no se asoció con aumento de la mortalidad ni con aumento del objetivo compuesto de mortalidad, rehospitalización o reintervención al año. La mortalidad total a los 30 días y al año fue del 2,2% y 14,6%, respectivamente.

Con el fin de intentar optimizar los resultados hemodinámicos en este tipo de procedimientos, Simonato y colaboradores estudiaron 292 casos incluidos en el *Valve-in-Valve International Data (VIVID) registry* para identificar los factores asociados con gradientes postprocedimiento elevados (gradiente medio ≥ 20 mm Hg)(163). La profundidad o altura del implante valvular se definió en relación al borde ventricular de la válvula quirúrgica previamente implantada. Para la válvula CoreValve Evolute (157 pacientes) una profundidad de implante de 4,52 mm mostró una sensibilidad del 91,3% y una especificidad del 29,5% respecto a la ocurrencia de gradientes postprocedimiento elevados. En consecuencia, se definió una implante alto como aquel que dejaba ≤5mm de la válvula transcatéter distal al borde ventricular de la válvula quirúrgica. Para la válvula Sapien XT (135 pacientes) una profundidad de implante del 11,8% de la longitud del stent mostró una sensibilidad del 88,5% y una especificidad del 32,2% respecto a la ocurrencia de gradientes postprocedimiento elevados. En consecuencia, se definió un implante alto como aquel que dejaba ≤10% de la longitud del stent distal al borde ventricular de la válvula quirúrgica. Los factores asociados de forma independiente con gradientes altos postprocedimiento fueron la altura de implante (siendo "protector" el implante alto: OR: 0,22, IC 95%: 0,1-0,2, p= 0,001), el tipo de válvula implantada (mejores resultados con la válvula Core Valve Evolut Vs Sapien

XT: OR: 0,5, IC 95%: 0,28-0,88, p= 0,02 y el mecanismo de fallo de la válvula quirúrgica (mayores gradientes post TAVR en pacientes con válvulas quirúrgicas degeneradas por estenosis/mecanismo mixto: OR: 3,12, IC 95%: 1,51-6,45, p=0,002). Con respecto a los mejores resultados hemodinámicos de la válvula Core Valve Evolut R, se cree que su diseño supraanular puede favorecer una mejor hemodinámica, sobre todo en este tipo de pacientes. Esta válvula también mostró excelentes resultados en pacientes ViV en comparación con la válvula Pórtico (164). Con datos de este mismo registro VIVID, utilizando un propensity score matching, se compararon los resultados clínicos y hemodinámicos de 54 pacientes tratados con la válvula Portico y 108 pacientes tratados con la válvula Core Valve. En el ecocardiograma postprocedimiento, el implante de CoreValve se asoció con una mayor área efectiva (1,67 Vs 1,31 cm^2; p=0,001), un gradiente medio más bajo (14,0±7,5 Vs 17,0±7,5 mm Hg; p=0,02) y menores tasas de IAo residual moderada o severa (4,2% Vs 13,7%; p=0,04). No hubo diferencias entre los dos grupos en la incidencia de complicaciones como mal posicionamiento de la válvula, necesidad de una segunda válvula u obstrucción coronaria. Aunque este estudio no tenía potencia estadística suficiente para detectar diferencias en objetivos clínicos, la mortalidad detectada al año fue superior entre los pacientes tratados con la válvula Pórtico (22,6% Vs 9,1%; p=0,03).

Además de una adecuada selección y posicionamiento del dispositivo, se han propuesto otras medidas para intentar optimizar los resultados hemodinámicos en pacientes sometidos a procedimientos ViV. Entre ellos, algunos investigadores han sugerido la posibilidad de realizar una valvuloplastia previa con un balón de alta presión que ocasione cierto grado de ruptura o distensión del stent de la bioprótesis quirúrgica previamente implantada. Si bien esto permitiría un aumento del diámetro interno de la prótesis quirúrgica, también podría aumentar el riesgo de complicaciones sobre el

anillo. Más interesante sería el incipiente desarrollo, de bioprótesis quirúrgicas con stents expandibles que permitirían optimizar los resultados hemodinámicos si después del SAVR se precisa de la realización de un procedimiento de TAVR ViV.

A la espera de estos nuevos dispositivos y en cualquier caso, creemos que los aspectos relevantes que se derivan de nuestro y de otros estudios respecto a los procedimientos ViV serían las siguientes:

- El TAVR en pacientes con antecedentes de SAVR es factible, seguro y se relaciona con adecuadas tasas de supervivencia a los 30 días y al año.
- Este tipo de procedimientos presenta características diferenciales respecto al TAVR en válvula nativa en cuanto a la incidencia de complicaciones. Estas diferencias fueron más evidentes en las primeras series e incluyen: mayores tasas de obstrucción coronaria y mal posicionamiento de la válvula (sobre todo en pacientes tratados previamente con válvulas "stentless"), gradientes residuales más elevados y menor incidencia de IAo residual.
- Es necesaria una adecuada planificación del procedimiento que incluya una adecuada selección del dispositivo y un cuidadoso posicionamiento del mismo con el fin de optimizar los resultados hemodinámicos y reducir la incidencia de complicaciones.
- Estos pacientes deben ser objeto de un seguimiento estrecho pues presentan una mayor incidencia de gradientes elevados postprocedimiento, de PPM, de DHV y, en algunos series de trombosis valvular subclínica.

Hasta el momento se han discutido aspectos relevantes referentes a la evolución hemodinámica post-TAVR, además de ello, consideramos crucial determinar los factores que conducen a un peor pronóstico clínico. Además de los objetivos de muerte

y ocurrencia de eventos cardiovasculares clásicamente estudiados en los diversos registros y ensayos, existe un creciente interés por concretar los factores asociados a una mayor tasa de rehospitalizaciones, sean o no de causa cardiovascular. Los procedimientos de TAVR se han llevado a cabo, tradicionalmente en pacientes de alto riesgo quirúrgico con numerosas comorbilidades asociadas, en los que las rehospitalizaciones después del procedimiento suponen un importante riesgo de aparición de nuevas complicaciones, así como un elevado coste económico asociado.

En nuestro estudio, que incluyó datos de 720 pacientes procedentes de dos centros, la incidencia de rehospitalización a 30 días fue del 14,6% y del 43,9% al año, respectivamente(165). Los predictores de reingreso hospitalario a 30 días fueron: complicaciones hemorrágicas durante el procedimiento (p=0,001), anemia (p=0,019), FEVI baja (p=0,042) y la prescripción conjunta, al alta, de terapia antiagregante y anticoagulante (0,014). Los predictores de rehospitalización al año, estuvieron menos relacionados con aspectos periprocedimiento y más vinculados a las comorbilidades basales de los pacientes: enfermedad pulmonar crónica (p=0,001), enfermedad vascular periférica (p=0,023), IRC (p=0,013) y fibrilación auricular (p=0,012). Además, los pacientes con ingreso en los 30 días post-TAVR presentaron mayor mortalidad durante el seguimiento (HR: 1,56; IC 95%:1,02-2,39; p=0,043). La etiología de los reingresos se repartió de forma balanceada entre causas no cardiacas (59%, entre ellas las más frecuentes las derivadas de patología respiratoria) y causas cardiacas (41%, entre ellas la más frecuente fue la insuficiencia cardiaca). En el momento de la publicación de nuestro estudio, los datos disponibles sobre el tema eran escasos, pero concordantes con nuestros resultados. Así, Holmes y colaboradores describieron una tasa de reingreso del 17% a los 30 días y del 53,2% al año(166). La relevancia de este estudio viene determinada por el elevado número de pacientes estudiados (12.182 pacientes incluidos

en el registro TVT) y por el hecho de que se tratase de pacientes que reflejan la práctica clínica habitual y no aquellos en el contexto de un ensayo clínico. Con posterioridad se han publicado otros registros en los que si bien la incidencia de reingreso a los 30 días no difiere significativamente, sí que se muestran una reducción importante en la tasa de reingreso al año. La **Tabla 6** resume los datos más relevantes de los estudios publicados posteriormente.

Primer autor	**n**	**STS (%)**	**Incidencia Reingreso 30 días**	**Predictores Reingreso 30 días**	**Incidencia Reingreso 1 año**	**Predictores Reingreso 1 año**
Kolte(167)	12221		17,9	IRC, ingreso TAVR>5 días, >4 Comorbilidades, EPOC,A.transapical, alta a institución.		
Holmes(166)	12182	7,1	17,4		53,2	
Panaich(168)	5702		21,3	IRC, EPOC, A.transapical, DM, alta a institución.		
Zweiker(169)	959	15,4			12	
Franzone(170)	868	6,6			25,4	Varón, IRC estadio 3
Nombela-Franco(165)	720		14,6	Sangrado, anemia, FEVI baja, ACO+antiagregante.	43,9	EPOC, IRC, FA, Enf Vascular periférica
Forcillo(171)	714	10	10,5	Anemia, válvula 23mm, duración ingreso TAVR.	18,8	AVC secuela permanente
Sud(172)	709	13	13,5		44	
Hannan(173)	389		18,8			

Tabla 6: Principales estudios valorando reingresos hospitalarios tras TAVR. ACO: anticoagulación oral; ACV: Accidente Cerebrovascular; DM: Diabetes Mellitus; EPOC: Enfermedad Pulmonar Obstructiva Crónica; FA: Fibrilación Auricular; FEVI: Fracción de Eyección del Ventrículo Izquierdo; IRC: Insuficiencia Renal Crónica; TAVR: Reemplazo Transcatéter de Válvula Aortica

Estas discrepancias en las cifras de mortalidad al año podrían deberse a discordancias a varios niveles(174):

-En el registro y definición de reingreso: en muchos estudios se consideran las hospitalizaciones cuando el periodo es superior a 24 horas de estancia, mientras que en otros no se considera la estancia en Urgencias aunque ésta sea superior al día.

-En la diferente organización del sistema sanitario entre los distintos países.

-En el perfil de riesgo y en las comorbilidades de los pacientes.

-En el protocolo de TAVR y en la duración de la estancia hospitalaria en el procedimiento índice.

-En los protocolos de seguimiento y manejo postintervención.

A pesar de posibles diferencias conceptuales o con respecto al perfil de pacientes, creemos que es preciso un estudio minucioso de los protocolos de los hospitales con menor tasa de reingresos con el fin de implementar las medidas necesarias para su disminución.

Además de los factores predictores anteriormente mencionados, existe un creciente interés por reducir el tiempo de hospitalización tras un procedimiento de TAVR. Estancias hospitalarias más reducidas, no sólo reducirían los costes del proceso asistencial , sino que también podrían traducirse en una menor incidencia de complicaciones postprocedimiento tales como las derivadas del decondicionamiento de los pacientes o las infecciones hospitalarias. Sin embargo, existe la preocupación sobre si una estancia hospitalaria acortada podría incidir negativamente sobre la necesidad de rehospitalizaciones. En este sentido, en estudio de Sud y colabores determinó que, tras ajustar por diferentes factores de confusión, no había una relación significativa entre una estancia post-TAVR corta y una mayor tasa de reingresos a 30 días o 1 año(172). Sí que se encontró una relación lineal entre las estancias prolongadas y las rehospitalizaciones al año, objetivándose un incremento de riesgo del 3% por cada día de duración adicional de la hospitalización en el procedimiento índice.

Otro de los interrogantes que surge es si las características, y sobre todo, la experiencia del centro en el que se realiza el procedimiento tiene repercusión sobre el pronóstico clínico en términos de necesidad de nuevos reingresos. A este respecto, Khera y colaboradores estudiaron a 129 hospitales que fueron divididos en función del número de procedimientos de TAVR en centros de alto (≥100/año), medio (50-100/año) o bajo volumen (<50/año) (175). Los reingresos durante los primeros 30 días fueron significativamente más bajos en los centros considerados de alto volumen (OR: 0,75. IC 95% 0,60-0,92 p=0,007). No hubo diferencias estadísticamente significativas en la duración de las rehospitalizaciones (p=0,74) ni en el coste de las mismas (p=0,63).

En resumen, consideramos que de nuestro estudio y de los citados anteriormente, pueden extraerse las siguientes conclusiones prácticas:

-Es preciso unificar la definición de reingreso post-TAVR así como la clasificación de la etiología de las mismas.

-Se han identificado una serie de características tanto basales como de procedimiento y derivadas de la hospitalización índice relacionadas con una mayor tasa de reingresos. Los pacientes con estas características podrían beneficiarse de un seguimiento clínico más estrecho.

-De igual forma, los pacientes con una rehospitalización temprana también habrían de ser seguidos minuciosamente, puesto que los estudios objetivan que presentan más mortalidad.

-Sería preciso identificar las características diferenciales por las cuales los grandes centros presentan menor número de reingresos, con el fin de optimizar los protocolos de TAVR en todos los hospitales.

CONCLUSIONES

- El implante transcatéter de la válvula autoexpandible Portico produjo resultados hemodinámicos a corto plazo similares a los de la válvula balón-expandible Sapien XT en el tratamiento de pacientes con estenosis aórtica grave y anillo aórtico pequeño. Son necesarios estudios prospectivos con seguimiento a más largo plazo y en pacientes con anillo aórtico mayor para confirmar estos resultados.
- La ausencia de terapia anticoagulante al alta, los procedimientos ViV, un mayor índice de masa corporal y el uso de una válvula transcatéter de 23 mm se asociaron con mayores tasas de DHV post-TAVR. Diversos estudios prospectivos y aleatorizados ya en marcha habrán de determinar si un régimen antitrombótico específico post-TAVR es capaz de disminuir el riesgo de DHV.
- Los procedimientos de TAVR ViV son factibles, seguros y se asocian con buenos resultados clínicos. Pese a ello, se asocian a una serie de riesgos específicos que han de ser tenidos en cuenta en la planificación del procedimiento y seguimiento de estos pacientes: elevados gradientes residuales, obstrucción coronaria, dificultades en el posicionamiento y dudas sobre la durabilidad de la prótesis a largo plazo.
- La incidencia de reingresos hospitalarios tras un procedimiento de TAVR es alta. Las causas de rehospitalización se repartieron entre etiología cardiaca y no cardiaca; la IC y la patología respiratoria, fueron las causas más frecuentes en cada grupo, respectivamente. Los reingresos tempranos se asociaron mayoritariamente con eventos de sangrado y anemia periprocedimiento mientras que los tardíos se relacionan, mayoritariamente, con comorbilidades basales de

los pacientes. La ocurrencia de rehospitalización temprana se asoció con una mayor mortalidad durante el seguimiento.

CONCLUSIONS

- Transcatheter aortic valve implantation with the self-expanding Portico system yielded similar short-term hemodynamic performance compared with the balloon-expandable SAPIEN XT system for treating patients with severe aortic stenosis and small annuli. Further prospective studies with longer-term follow-up and in patients with larger aortic annuli are required.
- The lack of anticoagulation therapy, a valve-in-valve procedure, a greater body mass index, and the use of a 23-mm transcatheter valve were associated with higher rates of VHD post-TAVR. Further ongoing prospective studies are required to determine whether a specific antithrombotic therapy post-TAVR may reduce the risk of VHD.
- Valve-in-Valve procedures are feasible, safe and are associated with good clinical outcomes. Nevertheless, there are several concerns that must be taken into account when planning the procedure and follow-up of these patients: high residual gradients, coronary obstruction and difficulties in valve positioning. Also, the long term durability of transcatheter aortic valve after ViV procedures needs to be assessed.
- The readmission burden after TAVR in an all-comers population was high. Reasons for readmission were split between non-cardiac and cardiac causes, with respiratory causes and heart failure as the main diagnoses in each group, respectively. Whereas early readmissions were mainly related to periprocedural bleeding events and anemia, most late readmissions were secondary to baseline patient comorbidities. Early readmission was an independent predictor of mortality during the follow-up period.

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ANEXO I

Casares, Laura (ELS-BCL)<l.casares@elsevier.com>

jue 01/06/2017 17:46

Para:María Del Trigo <mariadeltrigo@hotmail.com>;

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